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This draft report is a comprehensive summary and compilation of the scientific evidence related to the hypothesis that cancer rates in human populations are associated with their exposure to pollutants present in the ambient air. Critical comments on the strength and weaknesses of the studies are presented and general methodological problems in the conduct and interpretation of the studies are discussed. No overall judgments about the weight of the entire body of scientific evidence are presented. This draft is being circulated for technical review and comment.

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REVIEW AND EVALUATION OF THE EVIDENCE FOR CANCER ASSOCIATED WITH AIR POLLUTION

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DISCLAIMER

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PREFACE

This report has been prepared for the Office of Air Quality Planning and Standards (OAQPS), U.S. Environmental Protection Agency. An earlier version of this report was prepared for OAQPS in 1981. The report dated October 27, 1981 was revised to take account of criticisms and suggestions generated during an extensive peer review, and to incorporate new material published during 1981 and 1982. A draft version of this report was submitted to OAQPS on December 15, 1982. The December 1982 draft has been further revised to take account of comments generated during an internal EPA review, but no new material has been added. This revised report is intended to be a comprehensive review of scientific data published through November 1982. The Agency invites all readers of this report to send any comments to Dr. Nancy B. Pate, Project Officer, Pollutant Assessment Branch, (MD-12), Strategies and Air Standards Division, Environmental Protection Agency, Research Triangle Park, N. C. 27711.

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EXECUTIVE SUMMARY

This report is a comprehensive summary and compilation of scientific evidence related to the hypothesis that cancer rates in human populations are associated with their exposure to pollutants present in the ambient air. Critical comments on the strengths and weaknesses of the studies are presented, and general methodological problems in the conduct and interpretation of the studies are discussed. However, no overall judgments about the weight of the entire body of scientific evidence are proffered.

Section I of this report is an introduction, which defines its purpose and scope. Scientific evidence on the association between air pollution and cancer is of three main types: epidemiological studies of factors associated with patterns and trends in cancer rates; experimental studies of the carcinogenicity and mutagenicity of substances and mixtures emitted into or extracted from the ambient air; and monitoring studies of the presence in the air of substances known to be carcinogenic. The existence and strength of the hypothesized association between air pollution and cancer have been subject to extensive scientific debate. One general problem is that a relatively small effect of air pollution is difficult to establish conclusively in the presence of larger (and variable) effects of cigarette smoking and other factors (e.g., diet and alcohol). Another is that most cancers have multiple causes, and there are conceptual and methodological difficulties in attributing cancers to more than one causative agent in the presence of interactions. A third problem is that air pollution is complex and variable in constitution, and is difficult to characterize adequately from existing types of monitoring data.

Chapter II summarizes epidemiological studies of cancers in the human population and their relation to air pollution and other factors. Section II.B introduces the four principal types of epidemiological study and discusses issues that arise in applying them to the cancer/air pollution problem. Although there is evidence that air pollutants may affect cancers at a number of anatomic sites, only lung cancers have been studied in sufficient detail for critical analysis. Air pollution is a complex mixture of agents, and most available measurements are of conventional pollutants which are unlikely to be carcinogenic in themselves; furthermore, the use of a single component, such as benzo]a[pyrene, as a surrogate measure of the carcinogenic potential of polluted air may not be entirely satisfactory. Significant exposure to some air pollutants occurs in indoor environments, where monitoring data are scanty. The long latent periods for human cancers mean that current cancers should be associated with exposures in past decades, when some pollutants were present at higher levels and others at lower levels. The most pervasive difficulty encountered in the conduct and interpretation of epidemiological studies is the control of confounding factors, especially cigarette smoking. Other problems that

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arise include the interpretation of sex and racial differences in patterns of cancer mortality, the insensitivity of many studies, and the selection of appropriate comparison populations.

Section II.C summarizes source-specific or "neighborhood" studies. A number of studies have reported apparent elevations in cancer rates in the vicinity of industrial facilities of various types. Some of these studies were of the large-scale "ecologic" type, whose results are usually regarded as no more than suggestive. Most other studies in this category had substantial limitations, including problems in identifying appropriate control populations, in controlling for smoking, occupation, and demographic factors, and in verifying exposure. The more persuasive evidence of this kind is the finding of rare types of cancer characteristic of exposure to vinyl chloride and asbestos near putative sources of these materials, and the statistical association in several studies between lung cancer rates and proximity to smelters and other facilities handling arsenic compounds.

Section II.D summarizes several studies that suggest that migrants from one country to another with higher (or lower) air pollution levels continue to experience cancer rates characteristic of their native countries. However, the rigor of the statistical comparisons of cancer rates is questionable, and the differences were not related to specific data on exposure to air pollution.

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Section II.E summarizes urban-rural and other geographical studies. Table II-1 (Appendix A) tabulates 44 epidemiological studies of cancers of the lung and other sites in human populations. In 25 of these studies, a statistical association was reported between cancer rates and one or more (direct or indirect) measures of air pollution, and most of the rest reported excess frequencies of cancer in urban areas relative to rural areas. Only five studies reported finding no association between cancer rates and either urban location or measures of air pollution. However, all the studies were subject to various limitations, which complicate their interpretation.

The most pervasive and difficult problem in these studies is control for the confounding effects of cigarette smoking. Ten studies of lung cancer rates in nonsmokers have shown rather consistent urban-rural differentials in males, but not in females. However, all but one of these studies were limited by small sample size, and none was controlled for occupational exposures. In a number of studies, urban/rural differentials and statistical associations between cancer rates and air pollution remained significant after attempts were made to control for the effects of smoking, using data on smoking habits in cancer victims or population groups. However, the completeness of the control for smoking in these studies is disputed. Some scientists have argued that differences in aspects of smoking such as age at starting to smoke and depth of inhalation cannot be controlled for. However, actual data on these aspects of smoking do not confirm that they would contribute significantly to urban/rural differentials.

Only a few studies have been controlled for the effects of occupational exposures. One study that was so controlled revealed significant urban/rural differentials in both occupationally exposed and unexposed groups, after controlling for smoking. Other studies have suggested interactions between effects of occupation and air pollution.

Chapter III compiles and summarizes experimental evidence and monitoring data. A substantial number of studies has shown that extracts of airborne materials from polluted air and materials emitted from motor vehicle engines and stationary sources are frequently carcinogenic and mutagenic when tested in experimental bioassay systems. Results of in vivo tests have included the induction of skin cancers, lymphomas, fibrosarcomas, liver tumors and lung tumors in mice, lung tumors in rats and hamsters, and chromosome damage and sister chromatid exchange in hamsters. Respiratory irritants present in polluted air may also enhance the effects of other carcinogenic agents. Results of in vitro tests have included the induction of point mutations in bacteria and *Drosophila melanogaster*, malignant transformation of mammalian cells in culture, and sister chromatid exchange and DNA fractionation in cultured mammalian cells, including human cells. Positive results in these in vitro tests are generally correlated with the potential for carcinogenicity.

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Table III-1 (in Appendix B) lists more than 50 chemicals that have been detected in ambient air and that are known or suspected to be carcinogenic in humans or in experimental animals. Where comparative data are available, concentrations of these chemicals tend to be higher in urban areas than in rural areas, and higher still in industrial emissions. There is evidence of significant multimedia exposure to several pollutants after their release into ambient air.

Chapter IV summarizes attempts to estimate the possible magnitude of the association between lung cancer rates and air pollution levels. For this purpose, the index of air pollution most commonly used is the average atmospheric concentration of benzo(a)pyrene (BaP). Use of this index, however, causes difficulties because average levels of BaP in the United States have declined considerably since 1958 and probably were higher still prior to 1958. However, it is not clear that overall hazards posed by air pollution would have declined, since levels of other potential carcinogens have probably increased since 1940. BaP is thus not a stable index of the carcinogenicity of polluted air, and estimates made at one time period cannot be applied directly to others; for example, estimates based on study of lung cancers in the past cannot be used directly to predict future effects of current pollution.

Recognizing this problem, Table IV-1 tabulates 12 estimates of the quantitative relationship between lung cancer rates and air pollution levels as indexed by BaP concentrations.

Estimated slopes (regression coefficients) of this relationship range from 0.1-5.0 x 10^{-5} lung cancer deaths/year per ng/m^3 BaP. Some of these figures should probably be adjusted downwards by factors of 2 to 4 to take account of the likely reduction in BaP levels since the 1930s and 1940s when most effective exposures took place. The estimates derived from studies in the general population (0.8-5.0 x 10^{-5}) are significantly higher than those derived from studies of workers exposed to products of incomplete combustion (0.11-0.8 x 10^{-5}). This difference suggests that incomplete combustion products are associated with only part of the excess lung cancer rates observed in urban areas. Most of the studies were based on lung cancer mortality data from the 1960s, and the results are consistent with the hypothesis that at that time factors responsible for the urban excess in lung cancer were associated with about 11% of lung cancers in the United States. In the one study in which both cigarette smoking and potential industrial exposure could be accounted for, this estimate was about 17%. These quantitative estimates can be derived without resolution of the issue whether the unexplained urban excess of lung cancer can or cannot be attributed confidently to air pollution, which depends on interpretation of data summarized in Chapter II.

Several Appendices to this report deal with technical issues or tabulate information used in the text. Appendix E presents a calculation of the relationship between lung cancer rates and location of residence, after controlling for age,

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smoking, and occupational exposure. Appendix F discusses time trends in lung cancer incidence and mortality, including results from three recent cohort analyses which support the hypothesis that changes in smoking habits cannot account for all features or trends in the U.S. and the U.K. Appendix G presents a critique of two recent reviews of the subject that concluded that the association between air pollution and cancer rates was inconclusive or weak.

I. INTRODUCTION

The air contains a wide variety of hazardous substances, exposure to which may be associated with a broad range of adverse human health effects. Relatively high-level short-term exposures to some types of air pollution may result in acute sickness, alteration of important physiological functions, or impairment of performance. Prolonged exposure to lower levels may result in cancer or other chronic diseases, shortening of life, or impairment of growth or development.

During the past several years, the relationship between air pollution and cancer has received considerable attention. We have come to recognize a number of air pollutants as known or suspected carcinogens. Some of these are widespread and derive from a variety of sources (e.g., formaldehyde, benzene, asbestos, and certain polycyclic aromatic hydrocarbons), while others are limited to a few types of sources (e.g., certain chlorinated solvents or arsenic and other smelter emissions). The evidence for cancer risks associated with air pollution or specific pollutants in air is of three main types:

- Data from epidemiological studies, which include descriptive studies of trends in cancer by time, place, or affected group (e.g., sex, age, race); ecologic studies, which relate group differences in exposure to group differences in the frequency of cancers; and case-control or cohort studies, depending on whether the initial basis for study is a group of people with cancer (cases) or a group exposed to air pollution or another risk factor (cohort)

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- Data from laboratory studies, which include a range of in vitro studies (e.g., studies of the mutagenicity in cell cultures of substances identified in ambient air), and long-term carcinogenesis bioassays in animals of specific pollutants, complex mixtures of pollutants, or concentrates of air samples
- Data from monitoring studies, which involve measurements of individual pollutants in air and which are designed to demonstrate the presence of specific substances or mixtures, many of which may have been found to be cancer-causing in epidemiological or laboratory studies.

Some have interpreted this evidence as showing that cancer risks are associated with air pollution, while others have argued that the evidence does not support such an association. Although several surveys of the problem have appeared in recent years, (see Appendix E), no comprehensive review of the scientific evidence has yet been published. This report is intended to provide a compilation and evaluation of this evidence. Although we do not proffer an overall judgment as to the weight of evidence that air pollution (or specific pollutants) is associated with increased cancer risk, we point out the strengths, weaknesses, and biases of individual studies, and discuss a number of general problems in conducting and interpeting studies of this problem. At the request of EPA, this review covers all potential airborne contaminants except radioactive substances.

Much of the debate on this question has focused on urban-rural differences in cancer incidence or mortality, i.e., the observation of excess mortality from cancer at certain anatomic sites in urban compared to rural counties in the United States. Elevated cancer risks in urban areas, whether attributable to air pollution, cigarette smoking, occupational exposure, or other factors, are cause for concern among public health officials because over three-fourths of the population of the United States now lives in areas defined by the U.S. Census Bureau as urban. Furthermore, rural air in certain parts of the country may also contain carcinogenic pollutants, in which case urban risks calculated from urban-rural differences would tend to underestimate the role of air pollution, if carcinogenic air pollutants are in fact a cause of these differences.

In the debate on the relationship between air pollution and cancer in the United States, urban-rural differences have been interpreted by a number of scientists as evidence for an association. This has been supported by monitoring data that demonstrate the presence in air of substances previously shown in epidemiological studies (usually of workplace risks) or animal studies to be carcinogenic. Also, when controlled for other risk factors, urban-rural differences have been used to compute estimates of the magnitude of the risks posed by urban air pollution.

Other scientists have argued against the conclusion that an association exists because: (1) the evidence for increased cancer risks from urban air pollution is not consistent, in that some investigators have failed to final a correlation between lung cancer and measured levels of pollution; (2) urban lung cancer rates have not declined although air pollution, as measured by the level of benzo(a)pyrene (BaP), has declined; and (3) urban-rural differences have in some studies been observed only for men. These scientists have cited differing patterns of cigarette smoking, workers' industrial exposure, or both as alternative explanations for the urban-rural differences. Several scientists have argued that, in the presence of large and variable effects of cigarette smoking, it is impractical or impossible to detect smaller effects of air pollution, and that existing studies that appear to indicate such effects are inconclusive.

A. Nature of Cancer

Most experts now recognize cancer as a multicausal, multistage set of diseases (OSHA 1980). Cancer is a complex group of diseases that characteristically progress through a number of stages, each of which may be initiated or accelerated by a number of different intrinsic and extrinsic risk factors. Each factor may act at one or more stages, and different factors may interact in an additive or a synergistic (multiplicative) way. Furthermore, because of the frequently long latency period between initial exposure and manifestation of cancer, typically 20-30 years or more for many carcinogens, numerous opportunities exist for multiple exposures to potentially carcinogenic agents. It follows from the complexity of cancer causation and development that most cancers would have multiple "causes," and it would be simplistic to assign to any cancer or type of cancer a single causative agent.

The multistage, multicausal nature of cancer greatly complicates the task of identifying whether complex mixtures of substances, such as air pollution, cigarette smoke, and certain workplace exposures are associated with increased cancer risks. It offers, however, various opportunities for prevention, particularly when there is an interaction between risk factors.

B. Interaction Between Risk Factors

It is reasonable to expect that there will be interactions among cigarette smoking, air pollution, and other complex risk factors. First, many of the substances identified as carcinogens in cigarette smoke are also found often as pollutants in air or as constituents of emissions in the workplace. Second, synergistic interactions lead to a combined risk that is greater than the sum of the risks from each, in which case reduction in exposure to either factor is likely to be accompanied by a greater than proportionate reduction in risks. When two factors interact synergistically, each factor is not a confounding factor of the other, but an effect modifier (Rothman 1975). Synergism in the induction of lung cancer is known to occur in humans with a number of agents, e.g., between cigarette smoke and asbestos, and between cigarette smoke and radionuclides (Selikoff and Hammond 1975). In view of this, it is simplistic to attribute all lung cancers in which smoking is involved to cigarette smoking only.

Walker (1981) recently proposed a method for estimating the proportion of disease attributable to the combined effect of two factors. This method first identifies the etiologic fraction of disease due to the simultaneous action of both factors among exposed persons. This fraction is an estimate of the extent to which disease may depend on exposure to both factors together. An interaction index is then calculated, which is the proportion of disease attributable specifically to the interaction between two factors rather than to the disease expected from each acting alone.

As an illustration, if Walker's method is applied to the smoking, asbestos, and lung cancer data of Enterline (1979b) (see Table I-1), the etiologic fraction is 97%, i.e., the proportion of lung cancer among smoking asbestos workers attributable to smoking, asbestos, and their interaction, is 97%. (The remaining 3% is attributable to other, unidentified, factors.) Of the 97% attributable to smoking and asbestos, the proportion due specifically to interaction is 73%; the remaining 27% is expected from the effect of smoking and asbestos acting alone.

Another way of looking at interactions is to determine the proportion of cancers that could be prevented by eliminating either factor. This method attributes the interaction between factors to the factor being eliminated. This is illustrated in Table I-2 (OTA 1981), based on the data of Lloyd (1979), which are similar to those of Enterline (1979b).

The potential for interaction among cigarette smoking, air pollution, and other factors such as occupational exposure, requires careful evaluation. In such complex circumstances, attributing all possible disease to cigarette smoking whenever

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TABLE I-1

LUNG CANCER DEATH RATE BY SMOKING HISTORY
(Rates per 100,000 per Year)[a]

Cigarette Smoking	Asbestos Insulators	U.S. Males	Relative Risk
Yes	362.0	74.4	4.9
No	40.4	9.2	4.4

[a] If the combined effect of smoking and asbestos changes with age, the age distribution in the population to which these data are standardized will affect the calculations of the etiologic fraction and the interaction index.

SOURCE: Table 2 in Enterline 1979b

TABLE I-2

ESTIMATES OF PERCENTAGE REDUCTION IN LUNG CANCER MORTALITY IN ASBESTOS WORKERS BY ELIMINATION OF EXPOSURE TO CIGARETTES AND TO ASBESTOS

Status	Percentage Reduction from Current Rate
Current	0.0
Eliminate smoking only	88.5
Eliminate asbestos only	79.6
Eliminate smoking and asbestos	97.8

SOURCE: OTA (1981), Table 11, p. 68

cigarette smoking is a factor may lead to overestimation of the role of smoking and an underestimation of the importance of the other factors present. The implication for cancer prevention is that interference with any (or all) identified risk factors is likely to reduce disease incidence.

Synergistic effects between various substances, such as BaP and N-nitroso compounds, both of which are often present in ambient air, have also been demonstrated in animal experiments. In one such experiment, Montesano et al. (1974) instilled intratracheally into hamsters BaP adsorbed on ferric oxide particles. This was followed by repeated injections of diethylnitrosamine. BaP or diethylnitrosamine alone produced few malignant tumors, but the two in combination produced a 35% incidence of tumors, which appeared within a shortened latency period. In a similar experiment, Kaufman and Madison (1974) found that either N-nitroso-N-methylurea or BaP plus ferric oxide induced tumors with a latency of about 50 weeks after intratracheal instillation. When both substances were administered together adsorbed on ferric oxide, they caused a higher tumor incidence with a latency of 20-35 weeks. In another study, McGandy et al. (1974) examined the interaction of BaP adsorbed on ferric oxide, and polonium-210, a carcinogenic radioisotope. These substances were administered intratracheally in hamsters either simultaneously or sequentially. In both cases, the number of lung tumors observed was more than twice the number expected from the effects of each substance acting alone.

C. Nature of Air Pollution

Polluted air is a complex and highly variable mixture of substances. In many studies reviewed in this report, the term air pollution is considered synonymous with the air in areas with concentrations of heavy industry. Yet, since the days of the dial-painters, carcinogenic hazards have been known to exist in a number of light and service industries; because substantial strides have been made in the last two decades in reducing emissions from a variety of types of heavy industry, some of the most hazardous emissions may be from small, older operations that are not classified as heavy industry.

Data have been collected on a number of common, widespread pollutants, but the measurement of many pollutants is difficult and expensive. In many areas, only a fraction of the pollutant mixtures may be measured or even known. What is measured may not easily be generalized to other areas. Also, data that have been collected rarely cover the extended periods of time necessary for cancer to develop. Current levels of pollutants, often used as an indicator of past exposures, may not be representative of past exposures.

Even when the definition of air pollution is tied more closely to measured levels of specific pollutants, the results of a study can be substantially affected by the location, frequency, and extent of measurements. Pollution levels tend to drop off as distance from the source increases, and models of dispersion and movement are sensitive to a number of assump-

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tions about such factors as meteorological conditions and transformations of pollutants. If peak levels of a pollutant induce proportionately more damage than lower levels, the method of averaging over time as well as over distance can be important.

Thus, because of the complexity of cancer induction and the difficulty in knowing with any accuracy the exposure levels of a pollutant, the task of assessing whether and under what circumstances pollutants in ambient air may be associated with increased cancer risk is a complicated one. Air pollutants may act in several ways in the induction or promotion of cancer. First, substances emitted into ambient air may act alone to increase population cancer risks. This appears to be the case, for example, with vinyl chloride. Exposure to this substance in the workplace and perhaps in communities surrounding certain industrial plants increases the risk of developing angiosarcoma of the liver and possibly brain cancer. Second, ambient air pollutants may interact synergistically with other factors. The interactions between smoking and asbestos or radionuclides are prime examples of this. Third, substances present in the ambient air may also promote or otherwise enhance the carcinogenic effects of particular agents. The phenomenon of promotion or cocarcinogenesis among chemical agents has been studied in experiments with animal tissues (Sivak 1979). These experiments show that the effect of some carcinogens may be enhanced by other substances often present in polluted air (i.e., fine particulates and such respiratory irritants as sulfur dioxide).

Chemical carcinogens present as pollutants in air at low concentrations might be expected to have only slight effect by themselves but to have much greater effects when present in combination with these promoters or cocarcinogens. (There is also the possibility that substances in the air may act antagonistically, reducing the effectiveness of chemical carcinogens. This might be the case when carcinogenic pollutants are adsorbed to large, nonrespirable particulates.)

D. Purpose and Scope of this Report

The purpose of this report is to review in a systematic way the evidence for cancer risks associated with air pollution. First, we review the epidemiological literature on cancer risks associated with pollutants in ambient air, excluding radiation. The evidence has been divided into four major categories: source-specific studies, urban-rural comparisons, migrant studies, and time trend analyses. In reviewing this evidence, special emphasis has been placed on studies that were submitted to the record during the recent rulemaking on EPA's proposed airborne carcinogen policy. Second, we review the experimental and analytical data which indicate that ambient air may contain a wide variety of carcinogenic or mutagenic substances. A third section of this report reviews studies in which the possible magnitude of the association between air pollution and cancer rates has been estimated in quantitative terms. Summaries at the end of each section give an overall characterization of the extent of each type of scientific evidence and of the strengths and weaknesses of this evidence. However, no overall judgments about the weight of the entire body of scientific evidence are proffered.

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II. EPIDEMIOLOGICAL EVIDENCE

A. Introduction

This chapter reviews the epidemiological evidence for the proposition that ambient air pollutants contribute (either alone or in combination with other factors) to cancer rates observed in human populations. For purposes of this review, the chapter has been divided into four major sections (Sections B-E):

- Epidemiological considerations and issues
- Source-specific studies
- Migrant studies
- Urban-rural contrasts and other geographic studies, including attempts to correct or control for the contribution of other factors

Temporal trends in cancer rates are discussed in Appendix F, with a review of attempts to interpret them in terms of temporal changes in air pollution and in human exposure to other causative factors.

In the first section of this chapter (Section B), four major types of epidemiological studies that can be used to investigate the association of air pollution with cancer frequencies are described. The strengths and weaknesses of each type of study are described, and some specific problems that arise when they are applied to the air pollution/cancer problem are discussed.

In the second section, source-specific studies, i.e., studies that examine the relationship between air pollution

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from a particular industrial source and cancer rates in nearby communities) are reviewed. These include studies on the risks of cancer in communities surrounding several types of industrial facilities, such as smelters, asbestos factories, vinyl chloride manufacturing plants, and petroleum refineries. The strengths and weaknesses of each study are reviewed, including consideration of inconsistent data.

In the third section, studies of migrants from areas of high pollution to areas of low pollution (or vice versa) are reviewed. In the fourth section, urban-rural and other geographic comparisons are reviewed. In these studies cancer rates in urban (and/or industrial) areas are compared with those in rural (and/or nonindustrial) areas. The major problems with these studies are problems of confounding, i.e., differences in such factors as smoking and occupation that often exist between urban and rural areas. In this section we review attempts to isolate or control for the confounding factors and thus estimate the effects of air pollution, alone and in combination, in accounting for the elevated rates of cancer in urban areas.

Recent trends in cancer mortality and incidence are reviewed in Appendix F.

B. Epidemiological Considerations

Properly designed and controlled epidemiological studies can provide direct evidence that human exposure to a particular substance or pollutant is associated with a risk of disease. Such studies, however, are unfortunately vulnerable to many biases, leading to a wide range of limitations and uncertainties. Because of these limitations, the findings of a single study are rarely accepted as conclusive. Epidemiologic findings carry more weight when the results of independent studies conducted under different circumstances support each other. The results of epidemiologic studies may draw strength from, or may be challenged by, the results of other epidemiologic studies, as well as other types of scientific evidence.

Epidemiologic studies have been classified into four main types:

- Case reports
- Ecological or "descriptive" studies
- Cohort studies
- Case-control studies

The latter two types of study, which are also called "analytic" studies, carry more weight than the first two types because they are better controlled and usually reflect the consequences of exposure to specific individuals. Ecological and descriptive studies usually generate evidence of the circumstantial type and help to generate hypotheses about associations. Where the circumstantial evidence is very strong, they and certain case reports can lead to relatively firm conclusions. However, in most cases it is necessary to test the hypotheses generated by these studies, using the more rigorous methodology of cohort or case-control studies.

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1. Case Reports

Case reports take the form of reporting illness or death in one or several individuals--with the illness putatively associated with an exposure of an unusual type or a set of common exposures. Case reports often serve as the starting point in implicating specific exposures as possible causative factors. The hypotheses generated from these reports generally need to be tested systematically in controlled studies before they are regarded as conclusive. In some instances, when the effect is both pronounced and specific, such observations may provide strong evidence for an association between a substance and the outcome observed.

2. Descriptive Studies

Descriptive ("ecological") studies relate group differences in exposure to group differences in the frequency of disease. The groups typically comprise residents of geographical areas such as districts, cities, or counties. Data on geographical differences in cancer frequencies among these groups are related statistically to data on differences in exposure to chemicals or other possible causative factors. Other descriptive studies report trends in disease over time or by demographic characteristics (sex, race, income, etc.) and attempt to associate these with specific trends or differences in exposure. These studies generally use data that are readily available and thus may serve for preliminary examination of an hypothesis or to generate other hypotheses. Such studies often provide a basis for decisions on whether to initiate more intensive studies, and, more rarely, a basis for definitive conclusions about associations.

Ecologic and other descriptive studies are sensitive to misclassifications and the inappropriate handling of confounding factors. If sufficiently important, these may lead to underestimates, overestimates, or even reversals in the direction of a relationship between exposure and outcome at the individual level (Robinson 1950, Greenberg 1979). Results of these studies, therefore, are usually considered tentative until confirmed by other evidence. In evaluating the descriptive and ecologic studies bearing on the relationship between air pollution and cancer, the degree and manner in which potential confounding factors, such as age, sex, race, cigarette smoking and occupation, are taken into account influences the outcome.

Statistical sensitivity (the probability of detecting a true association when it exists) is an important concern in epidemiologic studies. Ecological studies usually are insensitive--or have a high noise-to-signal ratio. For example, sensitivity may be lost by considering all residents in a certain geographic area as "exposed." All residents are rarely equally exposed. If only a proportion of residents is actually exposed and at risk, the risk estimated in such a study will be diluted and may not even be detectable. Migration between geographic areas can also reduce sensitivity. As people migrate between areas, the distinction between exposed and unexposed is gradually lost. As a result, the ability of geographic studies to reveal an effect is likely to be reduced substantially if migration is not taken into account. The longer the cancer latency period, the larger this dilution effect is likely to be. It has been estimated that when migration has taken place over a 30-year period (roughly the latent period of the disease of concern), 40-50% of the actual excess risk will not be detected (Polissar 1980).

3. Cohort Studies

Cohort studies (and the case-control studies discussed below) measure the association between the risk of disease in individuals and their individual exposures to etiological factors. In cohort studies, a population of individuals is defined at the start of the study as being exposed, or "at risk", and is then followed over time in order to observe the incidence and timing of disease. A control population closely similar to the exposed population except for the exposure is established at the same time and followed in the same way. After a long enough time, incidence of disease in the two populations is compared.

The cohort approach is often used when the exposure under study is common. For example, with such risk factors as smoking or air pollution, large cohorts can be readily identified. However, when the number of exposed individuals is small, the combination of a small cohort and a relatively uncommon outcome (i.e., some specific cancer) can considerably reduce the statistical power of a study, and small-to-moderate associations

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generally will not be detectable. Schlesselman (1974) has shown that the sample size necessary to detect a twofold increase in lung cancer among exposed individuals (with a statistical confidence level of 95% that false positive results will not be accepted, and a statistical power of 80% that true associations will be detected) would require over 24,000 persons in both the study and comparison populations. Such large sample requirements often make it important that the power of a study, particularly one with "negative" findings, be carefully elucidated. Cohort studies are also subject to biases and confounding factors, unless detailed information about the characteristics and exposures of the cohort and control group is collected. These problems are especially important in retrospective cohort studies, i.e., studies in which a cohort is identified as it existed at some prior time, and its subsequent disease history is compiled.

4. Case-Control Studies

Case-control (or case-referent) studies work in the opposite direction from cohort studies (hence they are sometimes called "trohoc" studies, which is cohort spelled backwards). Cases (and appropriate controls) are identified, and an attempt is made to discover the extent of prior exposure in both groups. Case-control studies can usually be done much more quickly (and much more cheaply) than cohort studies, particularly where the disease (outcome) is rare. For relatively rare conditions, they are able to provide estimates of relative risk for exposed

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vs. unexposed persons. They usually cannot provide estimates of absolute risk, or the magnitude of risk that follows from a given exposure, although methods are being developed for estimation of exposure-specific rates (Schlesselman 1982). Case-control studies suffer from recall bias--i.e., people are asked to recollect exposures after the fact, and persons with a disease may probe their memories more deeply or more imaginatively in order to provide (for themselves) an explanation of their illness. These studies are also subject to distortion as a result of confounding, and are very sensitive (especially in their risk estimates) to the choice of appropriate controls.

A schematic for both case-control and cohort studies is given below:

	Disease		
Exposure	Present	Absent	Total
Present	a	b	m_1
Absent	c	d	m_2
Total	n_1	n_2	N

In the cohort study one defines at the outset the populations m_1 and m_2. After a suitable period of time an observation is made of a and c (b and d fall out automatically, by subtraction). The question is then asked:

$$\text{is } \frac{a}{m_1} > \frac{c}{m_2} \text{ ?,}$$

i.e., is the proportion of cases among the exposed greater than among the non-exposed?

In a case-control study, the comparison is usually made of $\frac{a}{b}$ (the "odds" that disease occurred in previously exposed persons) divided by $\frac{c}{d}$ (the "odds" that disease occurred in previously unexposed persons). The resulting "odds ratio", $\frac{a}{b}/\frac{c}{d} = \frac{ad}{bc}$, is an estimate of the relative risk to an exposed person. It does not matter that n_1 could be all persons (in a given hospital, say) with the disease and n_2 a sample of all persons without the disease. If the n_2 persons are appropriately chosen; the computation $\frac{ad}{bc}$ yields an unbiased result (Siemiatycki et al. 1981, Schlesselman 1982).

5. Issues Arising in Studies of Cancer and Air Pollution

In succeeding sections, we review a number of epidemiological studies in which the association between cancer and air pollution has been investigated. The results of 46 of these studies are summarized in tabular form in Appendix A (Table II-1). Most of these studies have been of the descriptive or ecologic type, but there have been several major prospective cohort studies (e.g. Hammond and Horn 1958, Hammond and Garfinkel 1980) and several large case-control studies in which large samples of lung cancer cases were compared to unmatched control populations (e.g., Haenszel et al. 1962, Dean et al. 1977, 1978). Many of the studies were not designed specifically (or exclusively) to investigate air pollution, and some merely provide evidence on urban/rural differences in cancer frequency.

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Seven general problems arise frequently in the interpretation of these studies, and will be discussed summarily at the outset.

a. Sites of action

Although some of the descriptive studies analyze data on cancers at a number of sites, most of the detailed studies are limited to lung cancers. The rationale for this focus (where stated) is that the lung is the primary site of contact with carcinogenic agents that may be inhaled from the ambient air, that lung cancer is the primary effect of cigarette smoking, that air pollution has components and characteristics in common with cigarette smoke, and that some evidence exists to suggest that air pollution may act to augment the effects of cigarette smoking (see *infra*). Although all of these points have some validity, there are several reasons to suspect that air pollution may also act at sites other than the lung. First, air pollutants (like cigarette smoke and other airborne carcinogens) come into direct contact with other organs, including the upper respiratory tract, the gastrointestinal tract and the skin. Second, cigarette smoking is associated with elevated cancer rates at sites other than the lung, including the mouth, pharynx, larynx, esophagus, pancreas, kidney, and bladder; indeed, for every excess lung cancer in cigarette smokers there is between 0.5 and 1.0 excess cancer at other sites (Doll and Peto 1981, Wilson 1980). Third, although the air pollutants that result from incomplete combustion include components that are found in cigarette smoke, ambient air also contains many other inorganic and organic carcinogens (see Chapter III below). Some of these are known to cause cancer in humans at sites other than the lung, including the skin, pleura, peritoneum, hematopoietic system, central nervous system, liver, and bladder (Althouse et al. 1980). Indeed, source-specific studies have yielded some evidence for excess frequency of cancers in the central nervous system, pleura, peritoneum, liver, lung, nasal cavity, skin, and breast in residents living in the neighborhood of industrial sources (for review see Section II-C below). Fourth, there is a marked urban excess of cancer at a number of anatomic sites, including sites not known to be affected by cigarette smoking or other identified urban factors (see Section II-E below). Finally, if air pollution acts to enhance the effect of cigarette smoking, it might well be conjectured that this enhancement takes place at sites other than the lung.

In principle, it would be desirable for these reasons to review and analyze studies of cancer frequencies at all sites where an association with air pollution might reasonably be hypothesized. In practice, data to support such an analysis are scanty and inadequate. Descriptive studies that suggest excess cancers at other sites are rarely controlled for smoking, and there is not enough quantitative information on the effects of smoking at other sites to attempt to subtract out its effects.

Accordingly, this review follows others in focusing on lung cancer.

Wilson (1980) suggested that, since cigarette smoking causes about one cancer at other sites for each lung cancer, it would be reasonable to assume that the same would hold for air pollution. Hence, he estimated the total number of cancers caused by air pollution by doubling his estimate for lung cancers. Although this assumption is probably more reasonable than ignoring other sites altogether, it is questionable for at least three reasons. First, more precise analysis of cancers attributable to cigarette smokng indicates that the ratio of excess cancer at other sites to excess cancers in the lung is between 0.5:1 and 0.7:1 rather than 1:1 (Doll and Peto 1981, Tables 10 and 11). Second, the dose-response relationships for airborne carcinogens at different sites may differ, so that the ratio for excess cancers at other sites to excess cancers of the lung observed in cigarette smokers may be too high (or too low) for persons exposed to lower concentrations of the same carcinogens. Third, as pointed out earlier, ambient air contains a wider variety of carcinogens than cigarette smoke, many of which act at sites other than the lung. Hence, Wilson's assumption may understate the likely risks at other sites. However, epidemiological data to investigate this hypothesis are very scarce.

b. Nature and measurement of air pollution

"Air pollution" is a complex and variable mixture of agents which exist in many chemical and physical forms, and no single measure of "air pollution" can suffice to characterize fully its potential to increase cancer risks. Unfortunately, most of the quantitative measures of "air pollution" levels that are available, particularly for the periods in the past when exposures are likely to have been most significant in causing current cancers, have been conventional pollutants, such as CO, SO_2, hydrocarbons, NO_x, ozone, etc., which are unlikely to be carcinogenic in themselves. These measures serve at best as indirect measures of fossil fuel combustion or industrial activity, and may or may not be well correlated with ambient levels of carcinogens. Other conventionally measured pollutants, such as total suspended particulate matter or "smoke," include products of incomplete combustion and are probably better correlated with at least one class of airborne carcinogen. However, neither these nor other available measures of air pollution have any direct relation to emissions or ambient concentrations of many of the inorganic carcinogens or industrial organic chemicals listed in Table III-1.

Estimating air pollution exposure involves (1) the selection of an appropriate indicator of the carcinogenic potential of air pollution, and (2) estimating the levels of exposure to that indicator. Ideally, one could then combine the contributions of each pollutant known or suspected to be related to lung cancer (see Table III-1, Appendix B). This would require a detailed historical inventory of the substances present in the urban atmosphere and their relative carcinogenic activity. Such information is not available. In its place several indicators of carcinogenic potential have been suggested. For example, benzo[a]pyrene (BaP), a product of fossil fuel combustion, has been used as a surrogate by several investigators.

The early choice of benzo[a]pyrene appeared to be reasonable in that BaP has been found to be carcinogenic and is relatively easy to measure. However, similar levels of BaP may occur with wide variations in the levels of other carcinogenic air pollutants. It has been shown that polynuclear aromatic hydrocarbons (PAHs) emitted from different sources are not in a constant relationship to each other or to BaP (Friberg and Cederlof 1978, Wilson et al. 1980). The use of BaP as a quantitative predictor of risk is discussed further in Chapter IV.

More recent work (Walker 1982) suggests that it may be possible to correlate health effects (lung cancer mortality) with the presence of mutagenic airborne materials. The short term mutagenesis tests, such as the Ames test, could be used to evaluate the mutagenic potency of air samples. This approach needs considerable development before it will become practical.

There are also problems associated with attempts to monitor exposure of the population to air pollutants. Monitoring is often done from a single sampling station in a community and measurements are used to characterize the levels of various pollutants in the surrounding census tract, city, or county. Any extrapolation from monitoring data involves some error, but when data from a few stations are used for a large area involving a diffuse population, the likelihood of substantial error is greater.

To remedy this would require detailed data on environmental release and behavior in relation to the size and characteristics of the exposed populations. The work of Greenberg (1979) indicates that the use of more refined estimates of exposure increased the strength of the association between industrial air pollution and lung cancer mortality. He found that total suspended particulate emissions, when corrected for land area and wind direction, showed a much higher correlation with lung cancer mortality than did the uncorrected emission figures.

The lack of information on cumulative exposure of individuals to air pollution is also a problem. This is particularly important with respect to cancer, in that incidence and mortality are in general proportional to cumulative exposure for many carcinogens (Schneiderman and Brown 1978). Only in situations where a single measurement of the indicator substance is proportional to the cumulative exposure to that material will the estimated relationship reflect the true effects of air pollution. Over the last 10 years, levels of many air pollutants have been declining (CEQ 1980). If this decline has been uniform throughout the country, then estimates based on current cancer mortality (affected by past air pollution levels) would over-

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estimate the role of air pollution. If, on the other hand, air quality was improving in some areas while declining in others (or improving at different rates), the full effect of air pollution would be underestimated.

c. Outdoor and indoor air pollution

Although the term "air pollution" usually connotes pollution of outdoor air, it has recently been recognized that human exposure to many airborne pollutants is often greater indoors, even in nonoccupational settings. Although systematic measurements of indoor air pollution are scanty, it appears that ambient concentrations are generally greater outdoors than indoors for pollutants that are emitted into or produced in the ambient air (e.g., SO_2, photochemical oxidants, and industrial chemicals), but are generally greater indoors for pollutants that are released or concentrated indoors (e.g., cigarette smoke, wood smoke, radon, formaldehyde, asbestos, and components of consumer products) (for a recent review, see NRC 1981). Since most people (other than outdoor workers) spend much more time indoors than outoors (Szalai 1972), indoor exposures are potentially very significant. Two studies which indicated excess frequencies of lung cancer in nonsmoking wives of smoking husbands (Hirayama 1981, Trichopoulos et al. 1981; but see Garfinkel 1981b for conflicting data) suggest that indoor exposure, at least to components of cigarette smoke, may be sufficiently high to lead to measurable increases in cancer risk.

In the absence of systematic monitoring or epidemiological studies of indoor exposure, it is only possible to speculate about its likely contribution to the results of the epidemiological studies reviewed in this section. For pollutants that are generated outdoors, concentrations are frequently lower indoors; for example, Wilson (1980) estimated that average BaP levels indoors would be only about 40% of those outdoors, so that risks posed by BaP to the average person would only be about 60% of those calculated on the basis of outdoor levels. Hence, it seems reasonable to assure that for these pollutants differences in exposure between polluted and unpolluted areas would be reduced in magnitude, in proportion to the time spent indoors. For pollutants that are generated indoors, it seems reasonable to assume that indoor concentrations would be relatively independent of geographical location, degree of urbanization, and degree of industrialization. For both reasons, we expect that indoor exposures would be more likely to dilute than to enhance the effects of outdoor air pollution in leading to geographical and urban/rural differences in air pollution. However, direct study of this issue is needed to confirm this expectation. One limited exception to this generalization is the indoor exposure of nonsmokers to cigarette smoke: to the extent that smoking is (or was) more prevalent in urban areas, urban nonsmokers might be at correspondingly greater risk.

d. Latency period and trends in exposure

A complicating factor in studies of the association between air pollution and cancer--as in all epidemiological studies of factors associated with cancer--is the long latency period that usually elapses between exposure to carcinogenic agents and the clinical manifestation of the resulting effect.

For most carcinogenic agents the minimum latent period before excess cancers can be observed is 20-30 years, and for agents such as asbestos the effective latent period may be 45 years or more. This means that associations have to be estimated between present cancers and exposures far in the past. Unfortunately, systematic measurements of exposure to air pollutants were limited in extent and reliability in the period when they were likely to have been most significant in causing current cancers--the 1930s, 1940s, and 1950s.

A particular problem with air pollution is that its composition and distribution as well as its intensity has changed since this critical period of interest. One major recorded change is the reduction in concentrations of particulates, smoke, and SO_2 in cities, which has resulted from the reduction in the use of coal for space heating and the location of fossil-fuel-fired power plants in rural areas (CEQ 1980).

While this has resulted in a reduction in measured levels of BaP, the primary indicator of incomplete combustion, it has also led to a general reduction in urban/rural differentials. Since the 1940s there has also been a massive increase in production of synthetic organic chemicals, including volatile carcinogenic compounds that can now be found in ambient air (Davis and Magee 1979). However, this has been accompanied by a general improvement in industrial hygiene, housekeeping, and pollution control, and by substantial efforts to reduce the emissions of agents known to be carcinogenic, such as asbestos and vinyl chloride. The consequence of all these changes is that reductions in ambient levels of some carcinogenic agents have been offset by increases in others, so that it is not possible to determine even the direction of trends in the likely overall risks posed by ambient air. However, it appears likely that the early control of combustion sources means that BaP is now less useful as a surrogate measure of the potential carcinogenicity of ambient air, since its reduction has been accompanied by the introduction of other (and more uniformly distributed) pollutants.

e. Sex and racial differences

Most of the studies reviewed in this report have been limited to (or focused upon) lung cancer in white males. In principle, useful information could be derived from sex and racial differences in cancer frequencies and patterns. For example, lung cancer rates in black males are higher than those in white males, although the former smoke less; this suggests that black males are either inherently more susceptible or are exposed more to other carcinogenic agents. Also, urban/rural differences in lung cancer rates are smaller in white females than in white males, even when crudely matched for smoking habits; this has been used to argue that the unexplained differences must be due to occupational exposures in the males. However, females also have substantial exposure to potential carcinogens in the workplace, and it has not been shown that the difference in their exposure is sufficient to explain the differences in their patterns of lung cancer. Another explanation of this difference is that females spend more time indoors in nonoccupational settings (Szalai 1972), so that they would be less exposed to urban/rural differentials in outdoor air pollution. A third possibility is that females are intrinsically less susceptible than males to carcinogens in the urban environment, because of hormonal or other factors. Although we comment on these and other features of some of the studies under review, in general the studies of blacks and females have not been sufficiently rigorous to yield the precise information that could be derived from them.

f. Confounding and effect modification

The most pervasive difficulty encountered in the conduct and interpretation of epidemiologic studies reviewed here is the control of confounding (Rothman and Boice 1982, Schlesselman 1982). In the present context, confounding is the influence of an extraneous variable that may wholly or partially account for an observed effect of air pollution or may mask a true association between air pollution and lung cancer. A confounding variable is an extraneous variable that satisfies both of two conditions (Schlesselman 1982):

1. it is a risk factor for lung cancer;
2. it is associated with exposure to air pollution, but it is not a consequence of that exposure.

An obvious example of a confounding variable in epidemiologic studies of lung cancer and exposure to air pollution is age. The risk of lung cancer increases with age, and sizeable differences in the age distribution between "exposed" and "unexposed" groups (or between cases and controls) could result in a spurious association if the "exposed" group contained older individuals than the "unexposed" group. Similarly, if the "unexposed" group contains older individuals than the "exposed" group, an association may be masked. For these reasons, epidemiologic studies of air pollution and lung cancer generally control for age differences, either by stratifying data according to age or by standardizing to a reference population with a specific age distribution. Other risk factors for lung cancer that may be confounding variables are cigarette smoking and occupational exposures to certain chemical or physical agents.

Confounding can be controlled by separating the effect of air pollution from the effect of confounding factors (Rothman and Boice 1982). Three strategies can be used for this separation: (1) strict matching of "exposed" and "unexposed" individuals or of cases and controls; (2) stratification according to levels or categories of the confounding factor, or (3) multivariate mathematical modeling. Strict matching is rarely possible, especially when large studies are undertaken, and it is employed only for certain case-control studies. With stratification, the comparison of "exposed" with "unexposed" groups (or of cases with controls) occurs within the various categories of the confounding factor. In each stratum, the confounding factor is set within a limited range so that the comparison will not be significantly confounded. When confounding is controlled by stratification, an overall measure of the effect of exposure can be obtained by taking a weighted average of the stratum-specific estimates. There are two basic ways of combining such data (Rothman and Boice 1982): pooling and standardization. An assumption in pooling is that differences among stratum-specific groups are due to sampling error. Standardization does not require such an assumption.

Stratification is often preferred to multivariate analysis because it permits closer examination of the data by the investigator and it is easier to interpret by readers (Rothman and Boice 1982). Multivariate analysis, on the other hand, reduces the investigator's "feel" for the data, involves a set of mathematical assumptions about dose-response and related relationships that can rarely be tested and verified, and its results are often difficult to interpret in direct epidemiologic terms.

A further complication in the control of confounding is the potential for interaction between a confounding variable (such as cigarette smoking) and a study variable (such as a measure of air pollution). If the effects of air pollution were enhanced in the presence of smoking, smoking would be an effect modifier for air pollution (and vice versa). Effect modifiers are not true confounding variables, and treating them as such could bias the estimate of effect and hence the conclusion about the nature and strength of an association.

In situations in which there may be several confounding factors, stratification may not be practical and multivariate analysis may be the preferred way to control several factors simultaneously. In addition, multivariate analysis may include various interaction terms in the event that some factors modify the effects of the exposure under study. The multivariate model can give an estimate of the importance of the interaction. Thus, multivariate analysis may constitute a more rigorous tool than stratification in the presence of interactions, but the results of such an analysis must be interpreted with care.

Most of the studies reviewed below employed stratification and standardization to control for confounding, but no study fully considered all potential confounding factors. Furthermore, a general limitation in these studies was the failure to consider interactions between study and confounding variables, or if considered, the informal nature of the analysis.

g. Study sensitivity

Several factors operate to reduce the sensitivity of many studies. Migration tends to blunt distinctions. Small studies are notoriously insensitive. For example, Winklestein et al. (1967), Dean (1966), and others, made computations on the basis of a small number of cases (often less than five). Conclusions based on such small numbers must be viewed with caution, in that the variability can be large and a few cases can substantially affect an apparent association. As with the failure to control for potential confounding factors, this could result in either an increase or a decrease in the observed associations. Dean (1966) reported that in inner Belfast the age-standardized lung cancer mortality rate for male non-smokers was 36 per 100,000 men. This was based on six cases. The upper and lower 95% confidence limits on this estimate (Table A-5 in Lilienfeld et al. 1967) are 78.5 and 13.2, respectively. For male non-smokers residing in the "Environs of Belfast," a lung cancer mortality rate of 16 per 100,000 men was calculated on the basis of one observed case. Upper and lower 95% confidence limits on this estimate are 89.1 and 0.4.

h. Comparison populations

Rural populations are often used as "control" or comparison populations. Rural residents are not without exposure to environmental hazards such as farm chemicals, pesticides, etc. Indeed, as pollution has become more widespread, the distinctions between exposed and unexposed populations have become blurred. Higginson and Muir (1979) noted this complicating factor:

> Often people assume that industrial and urban environments are more heavily contaminated by such agents as chemical carcinogens, mutagens, and promoters, and that comparison with nonindustrial areas should provide measure of their effect. However, these comparisons are complicated by widespread pollution by such chemicals as pesticides and herbi-

> cides occurring in modern agricultural societies as well as by behavioral and dietary variables.
> (p. 1992)

Shabad (1980) recently made the same point, noting the many sources of atmospheric benzo(a)pyrene and its ubiquitous nature in the environment. A recent analysis of cancer mortality data led Greenberg et al. (1980) to hypothesize that factors leading to environmentally induced cancer are diffusing, and are in turn leading to higher cancer mortality rates in parts of the United States other than the historically high rate areas of the Northeast and Great Lakes states. Blot and Fraumeni (1981) have reported on the recent great increase in lung cancer rates in both rural and urban areas of the southeastern United States. The rates in the southeast now exceed those in the northeast. Whether this is due to the rapid industrialization of the southeast following World War II (and possible concomitant increase in pollution) or to cigarette smoking differentials (if there are any) is not at all clear. It is thus unlikely that present urban/rural ratios provide a full statement of urban excess relative to a pristine environment. Future urban-rural differences may be even less.

C. Source-Specific Studies

The air in communities surrounding industrial point sources has often been found to contain carcinogenic substances. From this it has been anticipated that residents of such communities would be at increased risk of developing cancer. The issue discussed in this section is whether this risk is sufficiently large to be significant and measurable.

This local type of pollution (point source, source-specific, or neighborhood pollution) has been distinguished from pollution of the general ambient air derived from diverse sources. For example, Hammond and Garfinkel (1980) stated:

> General air pollution should be distinguished from "neighborhood pollution" of fumes or particulate matter from a factory or similar source. The effects of this type of exposure may certainly increase the risk of cancer in people living across the street from a factory from which chemical or mineral contaminations are discharged. But the effects of such risks for people living within several miles of such factories has not yet been clearly delineated.
> (at p.207)

Many carcinogenic substances have been identified through studies of work-place exposure; of the 36 compounds or processes that have been linked more or less strongly to cancer in humans, 23 are chemicals or processes identified in the workplace (Althouse et al. 1980). The impact of such substances may be restricted entirely to the workplace or may extend to the surrounding communities. Community or neighborhood studies are usually undertaken to see if they give results that are consistent with worker studies. Attention has been drawn specifically to studies of this kind that have reported associations of excess cancer with community exposure to arsenic, asbestos, and vinyl chloride (EDF/NRDC 1980).

Ambient community exposure levels are likely to be considerably lower than worker exposures, and the risks to individual persons are expected to be correspondingly lower. However, the differences in ambient concentrations are offset by several other factors. Ambient exposure may occur over a longer period of time (i.e., be of greater duration) than workplace exposure. The age at first neighborhood exposure may be considerably lower than at first workplace exposure. The population-at-risk may be larger for ambient pollution than for workplace exposure, and may include more highly susceptible individuals. Therefore, exposure levels that may have resulted in only a few cancers among a small worker population could theoretically lead to a substantial number of cancers among the larger (and more diverse) populations exposed to ambient pollution. However, any such effects would be more difficult to detect in the general population because of their low expected frequency and the difficulty in controlling for other factors.

1. Arsenic

Several studies have shown that workers exposed to high levels of inorganic arsenic are at an increased risk of developing lung cancer (Lee and Fraumeni 1969, Pinto et al. 1977, Ott et al. 1974). Because of these findings, several investigators have studied the risks to residents of communities in which smelting and refining industries are located. To date, the evidence is mixed for an association between cancer and community exposure to arsenic, some studies showing evidence for increased cancer risks, others not. Blot and Fraumeni (1975), Newman et al. (1976), and Pershagen et al. (1977) have reported that residents in counties in which smelters are located are at increased risk of developing cancer. Matanoski et al. (1981) have reported that lung cancer rates are significantly higher in areas near an arsenical insecticide plant. Similar increased risks were not found by Greaves et al. (1980), Lyon et al. (1977), and Perry et al. (1978).

Blot and Fraumeni (1975) studied the distribution of lung cancer mortality in 71 U.S. counties with primary smelting and refining industries. Using the data compiled by Mason et al. (1975), cancer mortality rates (for the period 1950-1969) were calculated for the white population in each county. Data on the possible confounding factors of population density, percentage urban, percentage nonwhite, percentage foreign born, median number of years schooling, median income, and geographic region were obtained from the 1960 census statistics.

A general linear, multiple regression model with adjustments for confounding was used to test for differences in cancer mortality between the smelting/refining counties and the remaining U.S. counties. It was found that lung cancer mortality, corrected for demographic variables, was significantly higher among both males (17%, $p<0.01$) and females (15%, $p<0.05$) residing in the 36 counties with copper, lead, or zinc smelting or refining operations than in counties without these operations. This excess was found in all counties independent of population size, but the magnitude of the excess was lower in the more populated, urban areas. The authors concluded that these

> ...findings suggest the influence of community air pollution from industrial emissions containing inorganic arsenic.

This interpretation of these results was questioned by ASARCO (1980), Air Products (1980), and AIHC (1981), who pointed out that Blot and Fraumeni failed to distinguish between smelters and refineries or between copper and other nonferrous smelters. In response to this criticism, Blot and Fraumeni's data were reanalyzed after eliminating the four counties containing only refineries. This recalculation did not substantially alter the results (EPA 1978).

A second criterism of Blot and Fraumeni's study was that most of the inhabitants in some of the counties did not live in close proximity to a smelter. However, this dispersion of population would be expected to have reduced the reported association by diluting the increased risks among those living close to smelter emissions with the larger numbers of persons residing far from the smelter and thus unexposed, or exposed to a lesser extent. The finding that lung cancer rates were only slightly elevated in the more heavily populated counties is consistent with this latter interpretation.

ASARCO (1980) also argued that the failure to control for smoking and occupational exposures could have resulted in a serious distortion of the results. However, as noted by Blot and Fraumeni, occupation is unlikely to be responsible for the elevated risks among females living in the counties; nor is it likely that the small fraction of the total male

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population directly employed in the smelting industry (less than 1% in over half the counties) would account for a 12-17% increase in total mortality from lung cancer. Smoking data collected by Newman et al. (1976) suggested that smoking habits among residents of smelting and refining counties were similar to national patterns. Thus, although rigorous control of these confounding factors was not attempted, there is no evidence that their effects would have been large.

ASARCO (1980) also argued that there is no statistical association between arsenic emissions from a given smelter (expressed in kg/hr) and lung cancer rates in the county. However, levels of human exposure to arsenic in a given county are a function not only of the rate of emission from the nearby plant, but also of the physical size (area) of that county, meteorological conditions, the location of the plant relative to the human population, and other factors that influence the level, duration, and nature of exposure. For example, the Tacoma, Washington smelter, which had the highest emission rate, is located in the northwest corner of a rather large county with much of the county population at some distance from the smelter; therefore, it is reasonable to assume that large numbers of residents were not exposed to arsenic or exposed to low levels. Also, the comparisons made by ASARCO (1980) did not take into account demographic differences between the various counties.

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Newman et al. (1976) studied the incidence and histologic types of bronchogenic cancer occurring among residents of Butte and Anaconda, two communities close to the Anaconda Copper Company smelter in Montana. Using data from the Montana State Register and the U.S. Census, incidence rates for lung cancer during 1969-1971 among men and women residing in Butte and Anaconda were calculated. These were compared to statewide incidence rates for all of Montana. It was found that the incidence of cancer of the bronchus and lung was significantly ($p<0.01$) elevated among men in both Anaconda and Butte, and among Butte women ($p<0.001$). Three respiratory cancer cases were found among Anaconda women, which was greater than expectation, but not statistically significant. When Newman et al. (1976) calculated the incidence of respiratory cancer among Anaconda women for a 10-year period of observation, they found that the Anaconda rate of 2.9 cases/10^4 persons was significantly higher ($p<0.05$) than the state rate of 1.4/10^4. However, this study did not control for smoking habits or for occupation, so it is not clear that the elevated rates were attributable to exposure via the ambient air.

Histological slides were available for 143 cases of lung cancer diagnosed between 1959 and 1972. These slides were re-evaluated by a panel of pathologists, and information on occupation, residence, and other factors was obtained for each case. Information on smoking habits was also obtained, but for only 41% of cases. The distribution of histologic types among four groups (copper-smelter workers, copper mine workers, "other" men, and women of Butte) was studied. Newman et al. (1976) reported a high percentage of poorly differentiated epidermoid carcinomas among smelter workers. This finding was consistent with similar reports of excess lung cancer of this histologic type among smelter workers (Lee and Fraumeni 1969) and patients receiving arsenic medication (Weiss et al. 1972). Poorly differentiated epidermoid carcinomas were also the predominant histologic type in female residents. Newman et al. concluded that arsenic must be strongly suspected as the etiologic agent of excess cancer in both the smelter workers (males) and in females in the general Butte and Anaconda populations. However, well differentiated epidermoid carcinomas were the predominant type in male residents of Butte and in miners, and Newman et al. suggested that these might have resulted from exposure to a specific type of friable sanding material used on the city streets during the winter months. Air Products and Chemicals (1980) also drew attention to the lack of excess cancers among residents of the counties surrounding Butte and Anaconda, but this does not conflict with the hypothesis of neighborhood effects.

Pershagen et al. (1977) studied the mortality from different causes in an area surrounding the Ronnskarsverken smelter works in northern Sweden. A reference population with a similar degree of urbanization, occupational profile, fraction of population working, and geographic location was chosen. For these two populations, causes of death over a 14-year period (1961-1974) were extracted from the National Registry on Causes of Death. The age structure of each population was derived from the National Censuses of 1960, 1965, and 1970. The standard mortality ratio (SMR) for lung cancer among males in the exposed population surrounding the smelter works was significantly ($p<0.01$) elevated when compared to that of the reference population. The SMR was not significantly elevated in contrast to national rates. Closer examination by Pershagen et al. (1977) of the 28 male cases with primary respiratory cancer revealed that 15 had been employed at the Ronnskarsverken smelter. Excluding these individuals, a nonoccupational SMR of 173 was calculated, which, although greater than 100, was reported to be not statistically significantly greater than national rates ($p<0.05$). Female lung cancer rates in the Ronnskarsverken area (relative risk = 1.08) were not significantly different from the national or comparison population rates.

There are, however, questions regarding the authors' statistical handling of these data. They calculated a (nonoccupational) SMR of 173 (13 observed vs. 7.5 expected) and reported that this was not significantly greater than 100. This difference is statistically significant ($Z = 2.01$, $p<0.05$) using a one-tailed test, which appears appropriate because the hypothesis under test is whether the SMR for males in the Ronnskarsverken area is greater than in the comparison area.

This study did not control for possible differences in smoking habits. However, large differences in smoking habits between the two local populations were considered unlikely because the two populations were similar with regard to the several socioeconomic variables to which smoking habits are closely related.

Lyon et al. (1977) investigated the incidence of lung cancer in communities surrounding a copper smelter near Salt Lake City. They identified all new cases of lung cancer during 1969-1975; all new cases of lymphoma were used as a control. Using addresses at the time of death or diagnosis, cases and controls were grouped according to position in relation to the smelter. There were no significant differences in the frequency of cancers between cases and controls at any specific distances from the smelter. The observed numbers of cases within four zones classified by distance from the smelter were all close to those expected. The authors concluded that these findings were not consistent with previous reports of increased rates of lung cancer among persons living near smelters.

Because of several features of this study, however, the authors' conclusion should be viewed with caution. First, the study was apparently not controlled for several potential confounding factors such as smoking and occupation. Second, the authors failed to consider migration in and out of the study regions. Third, the use of lymphomas as a control group appears to have been an inappropriate choice, since lymphomas have been associated with arsenic exposure (Ott et al. 1974). Finally, the study was conducted in a county in which the lung cancer mortality rate was one of the lowest of the 36 counties studied by Blot and Fraumeni (1975), and hence did not provide a sensitive test of their hypothesis.

Greaves et al. (1980) studied the incidence of lung cancer in ten communities surrounding nonferrous smelters. For the majority of these counties, the SMRs for lung cancer exceeded 100 (the range was 46-246). The authors identified all lung cancer cases (using as controls all cases of three other types of cancer: breast, prostate and colon) occurring between 1970-1977 within a 20 km radius of each smelter. Using addresses for each reported case at the time of death or diagnosis, the distance of the residence from each smelter was calculated for each case. The authors concluded there was no relationship between distance from the smelter and the incidence of lung cancer. However, some of the problems of potential confounding, interactions, and migration that were discussed earlier also apply to this study.

Matanoski et al. (1981) studied cancer mortality among residents of an area surrounding an arsenical insecticide plant in Baltimore. A significant excess of lung cancers was observed among males, relative to a comparison population matched for race, sex, age, and socioeconomic status. These comparisons were based on 25 lung cancer deaths. The excess in lung cancer remained when two lung cancer deaths among plant employees

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were removed. The remaining cases were distributed in an area lying north and east of the plant. This area had the highest levels of arsenic in the soil, which tends to confirm the fact of exposure. No significant excess was found in females. The interpretation of these results is complicated, however, by the lack of information on interactions with smoking or occupation. The lack of an effect among women suggests that other environmental or sex-specific factors (either acting alone or in conjunction with airborne arsenic) may be important.

2. Asbestos

A large number of investigators have demonstrated that occupational exposure to asbestos results in an increased risk of lung cancer, pleural and peritoneal mesotheliomas, and gastrointestinal cancers (IARC 1977). The indestructibility of this material, its wide use, and (at least in the past) large industrial emissions make it a reasonable hypothesis that such risks extended beyond the workplace. This is a particularly suitable example for study because two of the diseases associated with asbestos exposure (pleural and peritoneal mesotheliomas) are extremely rare in persons without exposure to asbestos, so that they serve as markers for asbestos-induced disease.

Several studies have reported apparent clusters or excesses of mesotheliomas in the vinicity of asbestos factories, mills, or mines. Newhouse and Thompson (1966) studied a series of 83 patients of the London Hospital with a diagnosis of mesothelioma in order to determine the extent (if any) of asbestos exposure. Full occupational and residential histories were obtained for 76 of these patients. Using 76 patients from the same hospital suffering from other diseases as controls, it was found that a significantly greater number of mesothelioma patients ($p<0.01$) with no evidence of occupational or domestic exposure were found to live within a half-mile of an asbestos factory.

This study has been criticized (AIHC 1981) for the choice of comparison groups. The controls, although matched for date of birth and sex, differed from the mesothelioma cases in that all were admitted to the hospital during 1964 while the mesothelioma cases were admitted between 1917 and 1964. This could be a source of bias because exposure conditions might have changed considerably between 1917 and 1964. Such biases would be expected to have reduced rather than increased the reported association, because the greatly increased use of asbestos would have made general population exposure to asbestos more common in 1964 than 1917, thus leading to greater potential for exposure in the controls than in the cases. The authors stated that there was no evidence that the controls were less likely than the study group to have worked in contact with asbestos or to have lived in close proximity to asbestos factories. However, the basis for this conclusion is not clear, especially for the persons who had died long before the study was conducted.

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Wagner et al. (1960) reported on 33 cases of diffuse pleural mesothelioma that were observed in South Africa during the years 1956-1960. All but one of the cases had probable exposure to crocidolite asbestos as a result of occupational exposure (4 cases) or residence near the Cape asbestos mine fields (28 cases). The authors reported that during the same period of time, diffuse pleural mesothelioma was rarely diagnosed in other (non-mining) areas of South Africa.

Although this study had no concurrent controls, the occurrence of diffuse pleural mesothelioma appears to be a sufficiently rare event that the results would undoubtedly be statistically significant if the population rates could be computed. Air Products and Chemicals (1980), in a critical review, raised the question of whether natural outcroppings and weathering of ore bodies could have been the source of asbestos exposure rather than mining activities. However, in either case it seems likely that airborne asbestos was the causative factor.

According to Bohlig et al. (1970), Dalquen et al. (1969) reported an increased incidence of mesothelioma in the neighborhoods surrounding an asbestos processing factory in Hamburg, Germany. Dalquen et al. (1969) reportedly found that while the total incidence of mesothelioma among the general population was 0.056% for the years 1959-1969, the incidence in the residential area near the factory was 0.96%. However, no test of statistical significance was reported. There are also several case reports (Tayot et al. 1966, Bohlig et al. 1970, Stumphius

1969, Wagner et al. 1971, and Tabershaw et al. 1970) of what appear to be environmentally related cases of mesotheliomas among residents in neighborhoods near shipbuilding areas.

Hammond et al. (1979), in the largest of the neighborhood studies, studied the mortality of residents in the vicinity of an asbestos factory in Riverside, a district in Paterson, New Jersey. From city directories for 1942-1954, all male residents of Riverside and Totowa, a second neighborhood which served as the control, were identified. These individuals were traced until 1976. During the period 1962 to 1976, no significant differences were noted in total deaths: 780 (43.8%) of Riverside subjects and 1735 (46%) of Totowa subjects had died. Specific causes were cancer at all sites: 163 (9.2%) vs. 353 (9.4%), and lung cancers: 41 (2.3%) vs. 98 (2.6%). One pleural mesothelioma in a Riverside male was reported in 1966. Although this single case is not sufficient to support the hypothesis generated by the case reports, the duration of follow-up may not have been sufficient to have detected environmentally-related mesotheliomas. Newhouse and Thompson (1965) found that the mean length of time between first exposure and death for mesothelioma cases living in the neighborhood of an asbestos factory to be 48.6 years (vs. 29.4 for factory workers).

Although the most extensive study was thus inconclusive, the rarity of mesotheliomas in individuals not exposed to asbestos gives considerable weight to the less well-controlled studies

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and case reports of mesotheliomas among residents in neighborhoods surrounding asbestos mines and factories. However, these studies yielded no specific evidence for exposure other than location of residence. Environmental exposure to asbestos also results from other activities (e.g., wearing out of brake linings in automobiles). In one study of urban dwellers, nearly all (96%) had asbestos fibers in their lungs (Churg and Warnock 1977). This suggests that asbestos from diverse sources, particularly airborne asbestos, may be an important problem for additional study.

3. Vinyl Chloride

Cases of the rare cancer, angiosarcoma of the liver (ASL), have been reported among individuals living near vinyl chloride fabrication, or polymerization, plants. Brady et al. (1977) studied the cases of ASL reported to the Tumor Registry of the Cancer Control Board of the New York State Department of Health during the years 1958-1975. For each of these cases a matched control with an internal malignant tumor other than primary liver cancer was selected from the registry. Cases and controls were matched on age (same 5-year age group), race, sex, county of residence, and vital status. Relatives of both the subjects and matched controls were interviewed in order to obtain information on potential exposure to vinyl chloride (VC), arsenic (As), or thorium oxide (ThO_2), as well as medical, familial, residential, and occupational histories. Of the 26 cases of ASL diagnosed during 1958-1957, 7 had direct exposure to VC, As, or ThO_2 ($p<0.02$). Of the remaining 19, 5 lived within one mile of a VC fabrication or polymerization plant. Although this is suggestive of an association, no statistical test of the possibility of this finding arising by chance was reported. Due to the small number of cases and the lack of monitoring data directly demonstrating exposure, no firm conclusions are possible.

Infante (1976) studied the mortality patterns of residents of four Ohio communities with polyvinyl chloride (PVC) production facilities. Using data for the Ohio white population as the standard, SMRs were calculated for central nervous system (CNS) cancer, leukemia and aleukemia, and lymphomas. He found that in these four communities the number of observed CNS cancers for both sexes combined during 1958-1973 was significantly greater than that expected (38 observed vs. 24.07 expected $p<0.001$). SMRs were also calculated for each of the counties excluding the areas surrounding the PVC facilities, but no significant excesses were found.

This study was reviewed by Air Products and Chemicals (1980), who commented that interpretation of this study is complicated by the fact that (1) the increase in CNS tumors was observed primarily in males, and (2) most of the excess occurred in one part of the study area (Painesville). They argued that these factors seriously challenge any conclusions of association of vinyl chloride with community cancer risks.

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To these criticisms should be added the failure to control for occupational exposure, race, and socioeconomic status.

Infante (1976) has also been criticized by the Society of the Plastics Industry (1980) for including North Ridgeville in the study group while not including other cities located as close as North Ridgeville or closer to the PVC facilities (e.g., Mentor, Ohio). If North Ridgeville is excluded from the study group, the excess in CNS tumors remains significant ($p<0.05$, one-sided test), however.

4. Petrochemical and Other Chemical Emissions

A number of studies have indicated that workers exposed to a wide range of industrial chemicals are at increased risk of developing cancer (Althouse et al. 1980). An increased risk of bladder cancer has been reported among workers exposed to benzidine (Case et al. 1954) and paints (Cole et al. 1972). Exposure to polycyclic aromatic hydrocarbons (found in crude petroleum, catalytically cracked oils, soot, and other pyrolysis products) has been associated with increased incidence of cutaneous and pulmonary cancers in workers (Doll et al. 1972, Lloyd 1971, Hammond et al. 1976, Fraumeni 1975).

Blot et al. (1977) studied cancer mortality patterns for 1950-1969 in the U.S. counties where the petroleum and petrochemical industries are most heavily concentrated. Using methods similar to those of Blot and Fraumeni (1975) described above, it was found that male residents of these counties experienced significantly higher rates for cancers of the lung, nasal cavity and sinuses, and skin compared to male residents of counties with similar demographic characteristics but with no petroleum industry. Lung cancer rates for white females in petroleum industry counties were also significantly elevated. Due to the lack of information on occupation and smoking, however, the specific reasons for these associations are ambiguous and somewhat debatable. Similarly, the causes of increased mortality rates for cancer of the bladder and liver among males and females (increased lung cancer mortality for males only) in U.S. counties with chemical industries are not identifiable without additional data. However, the finding of increased rates for both males and females suggests that factors other than occupational exposures are likely to be involved. Blot et al. (1977) noted that if occupational exposures in males and females were solely responsible for these increases, the worker risks would be substantially above those of the general population, and should be easily detectable.

Capurro (1979) studied the mortality experience of a population of 117 people exposed to solvent vapors from a chemical plant for more than 5 years. These individuals were followed for a 6-year period (1968-1974). During this time there were 14 deaths (vs. 6 expected), 7 of which were due to cancer. In particular, there were four cases of lymphoma (three reported on death certificates). The ratio of observed to expected deaths (based on Maryland death rates) was 3.0/0.0187 = 160. The incidence of new cases of cancer of the larynx was also elevated 61-fold (2 observed vs. 0.033 expected on the basis of incidence rates from the Connecticut Tumor Registry data). These high relative risks are based on few cases, and the authors noted that all four individuals with lymphoma were previously employed at a paper mill that closed in 1948. Questions also remain on the nature of the study population and the suitability of using state rates for comparison, particularly because two different sets of rates, Connecticut (for incidence) and Maryland (for mortality), were used.

Hearey et al. (1980) compared estimated age-adjusted cancer incidence rates (1971-1977) among Kaiser Foundation Health Plan (KFHP) members living near petroleum and chemical plants in the Contra Costa area of the San Francisco Bay region, to incidence rates among KFHP members living in the remainder of the bay area. Comparisons of rates for the two areas showed no evidence of increased cancer risk in KPHF members in the area near the plants. However, questions remain on the composition of the study population and whether the individuals enrolled in the KFHP were representative of the Contra Costa study population. It is unclear whether the controls were suitable for studying the relationship between industrial emissions and cancer. No adjustments were made to account for possible differences in occupation, duration of residence, socioeconomic status, and smoking, and it is not clear from the written report that the study was controlled for race. There is also some question whether there were sufficient differences in potential exposure levels between study and comparison populations to produce an effect large enough to detect.

5. Steel Manufacturing

Elevated rates of cancer have been reported in counties where steel is manufactured. Perry et al. (1978) reported that, among the female residents of Johnstown, Pennsylvania, the age-adjusted mortality rates of several types of cancer (oral, respiratory, breast, urinary, central nervous system, and peritoneal and other digestive system cancers) were significantly elevated over those of residents of the county living outside Johnstown. Rates in men, with the exception of digestive system cancers (and breast cancer), were also elevated in the community. Carnow (1978), in examining data from Allegheny County, Pennsylvania, and Lake County, Indiana, large steel production areas, also found increased lung cancer mortality rates among both males and females. Cecilioni (1972, 1974) analyzed the cancer mortality rates in Hamilton, Ontario, a steel manufacturing city, in 1966-1970. He found the highest rates in districts close to the steel mills. Similarly, Lloyd (1978) found significantly elevated lung cancer rates among male residents living near and downwind of a Scottish steel foundry in Scotland. This clustering could not be wholly accounted for by cigarette smoking or occupation.

D. Migrant Studies

This section summarizes several studies that have reported differences in site-specific cancer rates between native and foreign-born populations in South Africa, New Zealand, and the United States.

Haenszel (1961) found that mortality from lung and bronchial cancer was higher for English and German immigrants to the United States than for native Americans, but lower than the rates in their countries of origin. The results suggest that immigrants bring some of their greater liability to cancer with them, possibly because of living conditions experienced earlier. Yet, by leaving their native countries, they lose some of the still greater risk existing among people remaining at home. This might imply that migration involves reduction in exposure to some "native" carcinogens. Dean (1964) observed that the lung cancer rates for British subjects migrating to South Africa were intermediate between those of native-born South Africans and comparable to those of British subjects who remained in Great Britain. Eastcott (1956) found that immigrants from the United Kingdom had a 35% higher risk of lung cancer than native New Zealanders if they came from the United Kingdom before the age of 30, and a 75% higher risk if they migrated after the age of 30. The per capita consumption of cigarettes was higher in New Zealand and South Africa than in the United Kingdom. Differences in smoking habits are, therefore, not likely to account for these findings.

Among Norwegians living in Norway, where air pollution levels are generally low, the lung cancer rate is also low. Among the U.S. urban populations, where air pollution levels are higher, the rate is twice as high. For Norwegians who have migrated to the United States, the rate is midway between these (Reid et al. 1966).

In a study of male residents of Cuyahoga County, Ohio, the risk of lung cancer for Italian immigrants was found to be lower than that for U.S.-born residents and similar to the rate in their native country. Immigrants from England and Wales showed a lung cancer mortality that was similar to the rate for natives of the United States but lower than the rate for their peers in England and Wales (Mancuso and Coulter 1958; see also Mancuso and Sterling 1974). Adjustments for smoking were not made.

These studies of migrants suggest that early environmental exposure (in addition to smoking) is important in determining the risk of lung cancer later in life. In each of the studies discussed, the frequency of lung cancer among migrants is intermediate between the rates in the original country and the adopted country. The epidemiological evidence that risk is higher in migrants from countries with high pollution levels (and lower in migrants from countries with low pollution levels) is consistent with the hypothesis that polluted air is a contributing factor in the etiology of lung cancer.

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If it can be assumed that the exposure of emigrants from a particular country is representative of the general population exposure, these findings would indicate that long-term exposure to ambient air pollutants increases an individual's risk of lung cancer. However, there are several problems with the interpretation of these studies. First, it is not clear that the statistics on cancer rates in the different countries and on persons of different national origins in the same country were collected in the same way and were rigorously comparable. For example, in most studies cancer rates for immigrant communities were compared with national rates in their native and adopted countries. Second, none of the studies was controlled or even stratified for smoking habits, occupation, socioeconomic status, or urbanization in the country of origin. Migrants constitute self-selected populations that have experienced unsatisfactory conditions in their country of origin; it is a matter of conjecture to what extent these conditions may have involved occupational exposures, residence in polluted areas, or other factors that may have increased their cancer risks. Third, none of the studies reported actual measures of the air pollution levels to which the population groups were exposed, either in their country of origin or their country of adoption. Although it is a reasonable hypothesis that air pollution levels were generally low (in the relevant period prior to 1940) in New Zealand, South Africa, and Norway, intermediate in the United States, and high in Great Britain, there were presumably overlooked variations in exposure within each country. Thus, although these studies are consistent in suggesting that migrants from one country to another carry part of their risk with them, the studies do not permit rigorous tests of the hypothesis that early exposure to air pollution was a critical factor contributing to this risk.

E. Urban-Rural and Other Geographical Studies

1. Introduction

Geographical patterns of cancer have been studied more extensively than specific industrial emissions. Of particular relevance to the problem of air pollution and cancer is the comparison between cancer rates in polluted and nonpolluted areas.

Many such comparisons have been made, both directly and indirectly. For nearly all monitored pollutants, urban areas have higher levels of pollution than rural areas. If common constituents of air pollution increase the risk of developing cancer, it would be expected that cancer rates in polluted areas would be higher than those in areas with relatively little pollution (all other factors being equal). When rates in urban areas are compared to rates in rural areas, this is observed. A number of investigators (Table II-1, Appendix A) have reported that for lung and other forms of cancer, incidence and mortality rates are higher in urban areas than those in rural areas. For example, Table II-2 summarizes data on age-adjusted cancer

TABLE II-2

URBAN/RURAL COUNTY RATIOS OF U.S. AGE-ADJUSTED CANCER MORTALITY RATES, WHITE POPULATION, 1950-1969

Male		Female	
Site	Urban/ Rural	Site	Urban/ Rural
Esophagus	3.08	Esophagus	2.12
Larynx	2.96	Rectum	2.11
Mouth and Throat	2.88	Larynx	1.92
Rectum	2.71	Nasopharynx	1.66
Nasopharynx	2.17	Lung	1.64
Bladder	2.10	Breast	1.61
Colon	1.97	Bladder	1.58
Lung	1.89	Other Endocrine	1.52
All Malignant Neoplasms	1.56	All Malignant Neoplasms	1.36

SOURCE: Goldsmith (1980), Table 1, p. 206

mortality rates in the United States between 1950 and 1969. The ratios between overall rates in counties classified as urban and rural were 1.56 for all malignant neoplasms in males, and 1.36 for all malignant neoplasms in females; these ratios exceeded 1.5 at 10 individual sites (Goldsmith 1980). Table II-3 summarizes data from six studies of lung cancer mortality in the U.S. in the period 1947-51. Urban/rural ratios observed in these studies varied between 1.2 and 2.8 (Shy and Struba 1982). Table II-1 (in Appendix A) summarizes the results of 44 other studies, of which at least 39 reported higher rates of cancer in urban and/or industrialized areas than in rural and/or nonindustrialized areas.

So consistent are the findings of an urban-rural difference in cancer risk that no one seriously questions their validity, and most researchers speak of an "urban factor." However, when different researchers have tried to explain this urban factor or other geographical differences disagreements have arisen. Explanations of differences in terms of potential risk factors in addition to air pollution include smoking patterns, occupational exposures, population density, life-style, socioeconomic differences, and/or several other factors. In the following sections, we review the evidence for air pollution as a factor associated with geographical variations in cancer rates.

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TABLE II-3

THE URBAN FACTOR IN DISTRIBUTION OF LUNG CANCER MORTALITY IN THE UNITED STATES

Study, Geographical Area, Data Years, Age of Population	Lung Cancer Mortality by Urban and Rural Categories		Urban to Rural Ratio	Notes
Hoffman and Gilliam (1954) U.S. 1948-1949 All ages (age adjusted)	White Rates/10^5 Urban: 22.3 Rural: 12.3		1.8	Urban place = 2,500+ population
	Nonwhite Rates/10^5 Urban: 16.9 Rural: 7.3		2.3	
Griswald et al. (1955) Connecticut 1947-1951 All ages (age adjusted)	Male Rates/10^5			
	1. Cities 50,000+	31.2	1.75	1. U/R = 1 vs. 4
	2. Other metropolitan	23.1		
	3. Nonmetropolitan towns	28.3		2. Nonmetropolitan town = 2,500+ population
	4. Rural areas	17.8		
	Female Rates/10^5			
	1. Cities 50,000+	4.7	1.2	
	2. Other metropolitan	4.5		
	3. Nonmetropolitan towns	5.1		
	4. Rural areas	3.8		
		SMR		
Mancuso et al. (1955) Ohio 1947-1951 White males, 25-64 years	1. Metropolitan counties	123	--	SMRs are not directly comparable
	2. Other urban counties	82		
	3. Nonurban counties	69		

TABLE II-3 (Continued)

Study, Geographical Area, Data Years, Age of Population	Lung Cancer Mortality by Urban and Rural Categories		Urban to Rural Ratio	Notes
Zimmer and Haenszel (1956) Iowa 1950 All ages	Male Rates/10^5		2.7	Urban = town with 2,500+ population
	Urban: 32.8			
	Rural: 12.1			
	Female Rates/10^5		1.4	
	Urban: 9.0			
	Rural: 6.3			
Prindle (1959) U.S. 1949-1951 All ages (age adjusted)	Male Rates/10^5			
	1. Central SMSA counties	11.5	1.9	1. SMSA county = having a city of 50,000+ population
	2. Other SMSA counties	9.0		
	3. Non SMSA counties	6.0		2. U/R = 1 vs. 3
	Female Rates/10^5			
	1. Central SMSA counties	2.8	2.8	
	2. Other SMSA counties	1.4		
	3. Non SMSA counties	1.0		
Levin et al. (1960) New York State 1949-1951 All ages (age adjusted)	Male Rates/10^5			
	1. Metropolitan counties, urban	29.2	1.9	1. Urban = place of 2,500+ population
	2. Metropolitan counties, rural	23.9		
	3. Nonmetropolitan counties, urban	20.8		
	4. Nonmetropolitan counties, rural	15.2		2. U/R = 1 vs. 4
	Female Rates/10^5			
	1. Metropolitan counties, urban	3.2	2.8	
	2. Metropolitan counties, rural	3.5		
	3. Nonmetropolitan counties, urban	3.2		
	4. Nonmetropolitan counties, rural	1.3		

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2. Air Pollution as Factor in Geographical Variation in Cancer Rates

It is a plausible hypothesis that air pollution is responsible for some fraction of the urban factor or other geographical variations in cancer. As discussed in Chapter III, the urban atmosphere contains many chemical compounds, several of which are known to increase the risks of cancer among persons exposed to them in the work place or via personal exposure. Many other chemicals found in ambient air are known to cause cancer in experimental animals, and mixtures of pollutants extracted from ambient air have been found to be carcinogenic and mutagenic in experimental tests. The issue to be addressed is whether exposure of the general population is sufficient to lead to significant increases in cancer risk. This section of the report reviews the epidemiological evidence on this question--i.e., whether the effects that may exist are large enough to be detected against the variations in cancer rates imposed by other factors. Quantitative estimates of the possible magnitude of the contribution of air pollution are discussed in Chapter IV.

Table II-1 (in Appendix A) summarizes the results of 44 studies in which geographic patterns of rates of lung cancer and other cancers have been compared to geographic differences in air pollution and other risk factors. The most significant of these studies are also summarized and discussed in the text. In a number of studies, various measures of air pollution have been reported to be correlated with the geographic distribution of lung cancer, and these results are consistent with the hypothesis that air pollution is a factor. However, each individual study has had limitations that preclude a definitive test of this hypothesis. These limitations are also noted in Table II-1, and are discussed in the text.

The most common problems with most of these studies is the inability to control fully for factors that may confound or interact with ambient air pollution, such as industrial air pollution, cigarette smoking, or other personal exposures. As a result, the role of several factors known to be associated with cancer cannot be fully separated out to account for the "urban factor" in any individual study. Accordingly, scientific judgment on this issue has to be made on the basis of the weight of the evidence provided by a number of different studies in which separation of these factors can be made. In this section, we examine the potential differences in possible confounding factors and their relationship to observed geographical patterns of cancer incidence and mortality.

a. Smoking

Many of the studies of geographical variations in cancer summarized in Tables II-1 and II-3 did not take into account possible differences in smoking habits between the study and comparison populations. As a result, urban/rural differences in smoking patterns cannot be ruled out in these studies as a possible explanation of the urban factor. As mentioned in Chapter I and Chapter II.B, however, there are a number of

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ways in which smoking may interact with air pollution or other factors. When data on smoking habits were taken into account, smoking has usually been treated as a confounding factor. If there are synergistic interactions between smoking and another factor, controlling for the effect of smoking as a confounding factor would tend to overestimate the role of smoking and underestimate the role of any factor with which it interacts. Controlling for smoking tends to submerge the portion of cancers due to the interaction into the portion due to smoking acting alone (Walker 1981). Smoking was taken into account in several studies, however, and the corrected residual urban lung cancer rates were higher than those in rural areas (Dean 1966, Stocks and Campbell 1955, Dean et al. 1977, 1978, Hammond and Garfinkel 1980, Haenszel et al. 1962, Haenszel and Taeuber 1964, Buell and Dunn 1967). The main scientific issue to be discussed in reviewing these studies is whether the ways in which smoking was taken into account were sufficiently complete and precise to rule out smoking as a complete and sufficient explanation of the urban/rural difference (see Doll and Peto 1981).

The simplest, and possibly best, way to control for the effects of smoking is to limit the analysis to data on cancer in nonsmokers. One of the earliest available urban/rural comparisons of cancer rates has recently been presented by Logan (1982), who summarized and republished the results of a mortality survey conducted in England in 1881. A breakdown of comparative mortality by occupational status and by large districts yielded the following data on cancer rates (standardized per 1,000 cancer deaths in the total population):

All males	47
Occupied males	44
in London	59
in industrial districts	48
in agricultural districts	40

A similar survey conducted in 1901 led to similar results, with a ratio of 1.69 between cancer rates in London and in agricultural districts. These data are important because they refer to a period long before cigarette smoking became widespread; hence, the urban/rural differential cannot have been significantly affected even by passive smoking. (However, there was no control for occupation or other urban factors, and the reliability and completeness of diagnosis and data collection is not clear.)

Haenszel et al. (1962) and Haenszel and Taeuber (1964) obtained smoking and residence histories for a 10% sample of all lung cancer deaths in white females in the United States in 1958 and 1959, and for a 10% sample of all such deaths in white males in 1958. These data were compared to such information from a very large sample of the general population. Because of the large sample sizes, these studies provide the best available information on lung cancer by location of residence in nonsmokers (individuals who had never smoked). Furthermore, it is possible to control for the effects of migration by restricting attention to lifetime residents of either rural or urban areas.

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TABLE II-4

AGE-ADJUSTED LUNG CANCER RATES OF INDIVIDUALS WHO HAD NEVER SMOKED BY LOCATION OF LIFETIME RESIDENCE

	Males		Females	
Location of Lifetime Residence	Lung Cancer Mortality Rate/100,000	Relative Risk	Lung Cancer Mortality Rate/100,000	Relative Risk
Urban	12.5	3.2	8.4	1.7
Rural	3.9	1.0	5.0	1.0

SOURCE: Haenszel and Taueber 1964, retabulated by Pike and Henderson 1981

The results of this comparison are presented in Table II-4. Pike and Henderson (1981) suggested that the urban/rural ratio in men is spuriously high, because the lung cancer rate for rural men was actually lower than that in rural women. However, even the ratio in women is significantly higher than unity.

Shy and Struba (1982) summarized the results of six other studies in which lung cancer rates in nonsmokers were stratified according to location of residence. Another set of data is available from the study of Dean et al. (1977, 1978). These data are summarized in Table II-5. Five of these studies (Stocks and Campbell 1955, Dean 1966, Buell 1967, Hammond and Hova 1958, and Dean et al. 1977, 1978) showed a marked urban excess of lung cancers in nonsmokers, whereas two (Hitosugi 1968, Cederlof et al. 1975) did not. A general problem in interpreting these

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TABLE II-5

URBAN/RURAL DIFFERENCES IN LUNG CANCER MORTALITY RATES IN NONSMOKERS

Study, Data Years, Age of Population	Areas of Residence	Lung Cancer Mortality Rates per 100,000 Nonsmokers
Stocks and Campbell (1955)	1. Urban Liverpool	131
1952-54	2. Mixed	0
Ages 45-74	3. Rural	14
	Ratio 1:3	9.3
Dean (1966)	1. Inner Belfast	36
1960-62	2. Outer Belfast	40
Ages 35+	3. Other Urban	21
	4. Rural Districts	10
	Ratio 1:4	3.6
Hitosugi (1968)	1. High pollution	4.9
--	2. Intermediate pollution	3.8
Ages 35-74	3. Low pollution	11.5
	Ratio 1:3	0.4
Buell (1967)	1. Los Angeles	28
--	2. San Francisco Bay area	44
Age-standardized	3. All other counties	11
	Ratio (1+2):3	3.3
Hammond and Horn (1958)	1. US cities 50,000+	14.7
1952-56	2. US towns 10,000-50,000	9.3
Age-standardized	3. US towns <10,000	4.7
	4. Rural areas	0.0
	Ratio 1:4	X
Cederlof et al. (1975)	Males	
1963-73	1. Large cities	0
Age-standardized	2. Other towns	10
	3. Rural areas	16
	Ratio 1:3	0
	Females	
	1. Large cities	3
	2. Other towns	10
	3. Rural areas	16
	Ratio 1:3	0

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TABLE II-5 (continued)

Study, Data Years, Age of Population	Areas of Residence	Lung Cancer Mortality Rates per 100,000 Nonsmokers
Dean et al. 1978	Males	
	1. Eston	60
	2. Stockton	56
	3. Rural areas	35
	Ratio 1+2:3	1.7
	Females	
	1. Eston	15
	2. Stockton	19
	3. Rural areas	20
	Ratio 1+2:3	0.85

data is the low frequency of lung cancer in nonsmokers, which resulted in small numbers of cancer cases (see discussion above), and the wide variability in reported nonsmoker rates from study to study. Doll and Peto (1981: Appendix E) have drawn attention to variations in estimates of lung cancer rates in nonsmokers, which they attributed to confusion in some studies between ex-smokers and lifelong nonsmokers. However, the study of Haenszel and Taeuber (1964) was not subject to these limitations, because it was based on a large sample of lifelong nonsmokers. Hence, this study (Table II-4) provides the most compelling evidence for an urban/rural difference independent of smoking.

In evaluating the studies of geographical patterns of cancer rates in smokers, it is important to consider first whether urban-rural differences in smoking patterns do indeed exist and, if so, whether such differences have been of sufficient magnitude to explain the observed excesses in urban cancer mortality. It is generally agreed that cigarette smoking first became prevalent in cities (Doll 1978, Doll and Peto 1981, Wilson et al. 1980). There are very few quantitative data, however, on differences in the proportions of individuals who smoke or the number of cigarettes smoked. Doll (1978) referred to a survey done by the Tobacco Research Council, which indicated that in 1970 men and women residing in "conurbations" smoked twice as many cigarettes as men in "truly" rural parts of Great Britain. A 1955 national survey in the United States (Haenszel et al. 1956) also indicated that differences existed between urban and rural-farm residents (see Figure II-1). Doll and Peto (1981: footnote 37) cited without reference a survey conducted by Fortune magazine in 1935, which

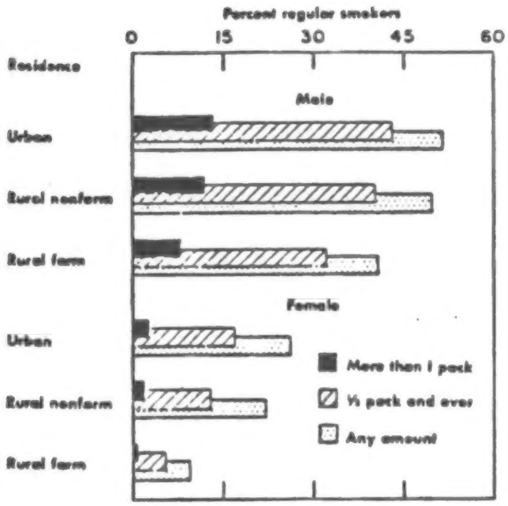
> ...found the respective percentages of men and women who smoked any form of tobacco to be 61 and 31% in large cities, as against 44 and 9% in rural areas. Since many rural men smoked only pipes and/or cigars (which have relatively much less effect on lung cancer than cigarettes), the urban-rural differences between the percentages who smoked cigarettes between World Wars I and II were probably very marked among the young of both sexes.

More recent data (Table II-6) indicate that the percentage of farm workers who are current, regular cigarette smokers is similar to that of white-collar workers (DHEW 1979). However, a higher percentage of blue-collar workers (craftsmen, operatives, and nonfarm laborers) is classified as current regular cigarette smokers. Also, men smoke more than women, although this difference is not as great as it was 20 years ago (USDHEW 1979), and many of the cigarettes advertised specifically for women contain less tobacco than the average cigarettes and are often also relatively low in tar. Current cigarettes contain substantially less tobacco per cigarette than did earlier cigarettes.

To consider whether these differences in the prevalence of smoking are likely to account for observed urban/rural differences in lung cancer mortality, we can follow the approach of Schlesselman (1978). To do this calculation, we assume that the relative risks of lung cancer mortality among males were 12 for current or occasional smokers and 6 for ex-smokers,

FIGURE II-1

PERCENTAGE OF PERSONS 18 YEARS OF AGE AND CURRENTLY SMOKING CIGARETTES REGULARLY, BY SEX, WITH ADDITIONAL DETAIL ON CURRENT DAILY RATE, FOR URBAN, RURAL NONFARM, AND RURAL FARM POPULATION



SOURCE: Haenszel et al. (1956), Figure 13, p. 30

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TABLE II-6

ESTIMATES OF THE PERCENTAGE OF CURRENT, REGULAR CIGARETTE SMOKERS, ADULTS AGED 20 YEARS AND OVER, ACCORDING TO FAMILY INCOME, SELECTED OCCUPATION GROUPS, AND MARITAL STATUS, UNITED STATES, 1976

Category	Male	Female
1. Family income		
Under $5,000	42.5	33.5
$5,000 to 9,999	42.5	32.5
$10,000 to 14,999	42.5	32.5
$15,000 to 24,999	40.4	33.0
$25,000 or more	34.7	35.1
2. Occupation groups		
White collar	36.6	34.3
Professional, technical, and kindred workers	30.0	29.1
Managers and administrative, non-farm	41.0	41.6
Sales workers	39.9	38.1
Clerical and kindred workers	40.4	34.8
Blue Collar[1]	50.4	39.0
Farm	36.9	31.3
Currently unemployed	56.8	40.0
Not in labor force	32.9	28.2
3. Marital status		
Never married	40.1	28.3
Currently married	41.1	32.4
Widowed	32.6	20.4
Separated	63.3	45.1
Divorced	59.9	54.8

---

[1] Craftsmen and kindred workers, operatives including transport, non-farm laborers

SOURCE: USDHEW 1979, p. A-16

(derived from data in USDHEW 1969, Chapter 5, Table 1). These assumptions are likely to overestimate the relative risks because they are similar to the values reported for male veterans (Kahn 1966), whereas Haenszel et al. (1956) found that veterans smoked more than males in the general population in all age categories. For women, we assumed that the relative risks for current or occasional smokers and for ex-smokers were 4.4 and 2.2, respectively. These too are probably an overestimate. For the proportions of smokers we used the data on whites of Haenszel et al. (1956), broken down by urban, rural nonfarm, and farm categories (Figure II-1). We weighted the rural categories according to their relative proportions in the U.S. population in 1960 (U.S. Bureau of the Census 1980, Deare 1981).

Using Schelesselman's (1978) Table 1, we obtained estimates of the urban/rural ratios in lung cancer rates that would be expected to result from 1955 differences in the prevalence of smoking, in the absence of any other urban/rural differences in risk factors. These estimates are presented in Table II-7, and are much smaller than the observed ratios tabulated in Table II-2. (The comparison is not precise, because the observed ratios are for the period 1950-69, whereas the smoking data are for 1955.)

There is a problem with the use of the Schiesselman approach, however. This formula for estimating spurious (confounding) effects is derived from the assumption that the several effects act independently. As discussed earlier--and in view of the

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TABLE II-7

ESTIMATED RELATIVE RISKS OF LUNG CANCER MORTALITY EXPECTED FROM DIFFERENCES IN THE PREVALENCE OF SMOKING IN 1955 BETWEEN URBAN AND RURAL POPULATIONS

	Observed Urban/Rural Ratio (adjusted for age but not for smoking)	Expected Urban/Rural Ratio (based on differences in smoking between urban and rural residents)
Men	1.89 (See Table II-2)	1.06
Women	1.64 (See Table II-2)	1.15

multistage theory of cancer causation--this is not likely to be true. In the presence of interactions, the Schelesselman formula will tend to overestimate the contribution of the confounder (in this case, smoking), but the precise contribution of the confounders to an apparent association cannot be calculated.

In addition to differences in the proportion of smokers and in the number of cigarettes smoked, Doll and Peto (1981) have drawn attention to the potential importance of other characteristics of smoking behavior:

> The reasons for uncertainty deserve some detailed discussion, for if they are overlooked a misleading impression of the hazards of air pollution may be engendered. The key observation is that lung cancer risks among cigarette smokers in middle and old age depend very strongly on the exact age at which cigarette smoking began. For example, delay of the onset of cigarette smoking in the late teens or early twenties by just a couple of years may reduce the risk of lung cancer at age 60 or 70 by as much as 20% (see text-fig. El on page 1292). Therefore, lung cancer risks in cities and in rural

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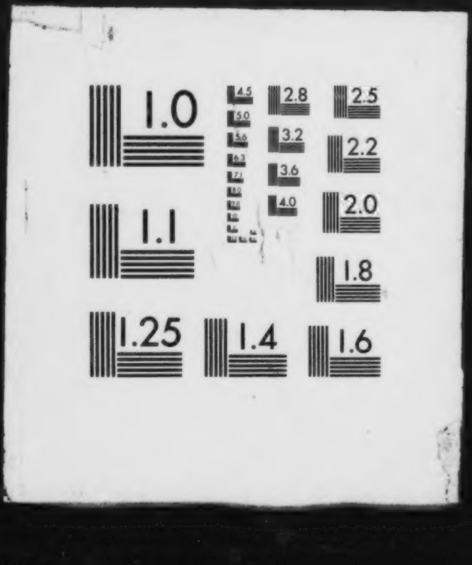
1.0
4.5
5.0
5.6
6.3
7.1
8.0
2.8
3.2
3.6
4.0
2.5
2.2
2.0
1.1
1.8
1.25
1.4
1.6

> areas depend strongly not only on what old people now smoke, but also on what they smoked in early adult life half a century or so ago. If cigarette smoking by young adults was somewhat more prevalent (in terms of percentages of serious cigarette smokers or numbers of cigarettes per smoker) in cities than in rural areas during the first half of this century, this alone would engender a substantial excess of lung cancer today when cigarette-smoking city dwellers are compared with cigarette-smoking country dwellers. The smoking of substantial numbers of cigarettes was an extremely uncommon habit in all countries in about 1900, while by 1950 it had become common throughout the developed world.
>
> While any new habit is in the process of becoming adopted by society (e.g., the use of various drugs today), it is likely that its prevalence among young adults will be greater in cities than in rural areas. In appendix E we discuss in detail the effects of differences in cigarette usage in early adult life on the lung cancer risks many decades later among men who would all, in later life, describe themselves as "long-term regular cigarette smokers of one pack of cigarettes per day." Because of such effects, one must anticipate, even if air pollution were completely irrelevant to the carcinogenicity of cigarettes, to find that urban smokers now have greater lung cancer risks than do apparently similar rural smokers, at least in studies of populations who still live in the type of area (urban or rural) where they grew up. This should, of course, also hold in countries other than the United States, and it is noteworthy that urban-rural differences in countries such as Finland and Norway where the cities have not been heavily polluted are of a similar size to the urban-rural differences in Britain and the United States.
>
> (pp. 1246-1247)

Doll and Peto also drew attention to effects of the amount of each cigarette that is smoked and the depth of inhalation (Appendix E). However, few data are available to test their hypothesis that urban/rural differences in age at starting smoking may have contributed substantially to urban/rural differences in lung cancer mortality.

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Haenszel et al. (1956) concluded that no important differences existed between urban and rural populations in age at starting smoking. The data of Haenszel et al., collected in 1955, are presented in Table II-8, and show no important differences between urban, rural nonfarm, and rural farm residents in the age distribution of starting smoking in any cohort of either sex.

In contrast to this, Weinberg et al. (1982) surveyed smoking habits in two areas of Allegheny County, Pennsylvania, and found substantial differences in this and other characteristics of smoking (Table II-9). These data support Doll and Peto's hypothesis that these characteristics of smoking vary in parallel with the prevalance of smoking. However, the two areas in Weinberg et al. were not urban and rural, but urban and inner suburban, and they were not an unbiased measure of geographical differences in patterns of smoking, because they were selected on the basis of having the highest and lowest rates of lung cancer in the county. Thus, data of Weinberg et al. appear to reflect socioeconomic differences in patterns of smoking and do not necessarily conflict with those of Haenszel et al. Dean et al. (1977, 1978) investigated patterns of smoking in urban and rural areas of northeastern England, obtaining data for lung cancer cases and controls on age of starting smoking, number of cigarettes smoked, types of cigarette, and inhaling habits. The results, reproduced in Appendix H, show no important differences between urban and rural areas in any of these aspects

TABLE II-8

CUMULATIVE PERCENTAGE OF PERSONS BECOMING REGULAR CIGARETTE SMOKERS PRIOR TO AGE SPECIFIED, BY SEX AND AGE, FOR URBAN, RURAL NONFARM, AND RURAL FARM POPULATION

	Sex and Age (years)											
	Males						Females					
Started Smoking Prior to Age	18-24	25-34	35-44	45-54	55-64	65+	18-24	25-34	35-44	45-54	55-64	65+
							Urban					
15	6.9	6.4	7.1	6.5	6.5	5.1	2.6	1.2	0.7	0.3	0.2	0.2
18	34.9	35.8	31.1	26.7	22.7	14.5	18.1	12.1	7.8	2.0	0.8	0.2
20	51.0	56.2	49.8	42.7	35.6	19.4	33.0	25.3	16.1	4.9	1.3	0.6
25		68.1	64.8	58.9	50.3	26.6		38.9	29.1	12.0	3.0	1.0
30		68.9	67.3	62.1	53.4	29.4		42.2	34.4	16.6	4.6	1.5
							Rural Nonfarm					
15	6.5	6.6	7.1	7.6	7.7	4.6	1.3	2.0	0.4	0.5	0.6	
18	33.1	36.8	32.4	32.2	25.9	14.6	12.7	12.6	6.7	2.6	0.9	1.0
20	49.9	54.9	50.0	48.5	40.1	19.0	24.2	23.3	14.3	5.7	2.2	1.2
25		65.7	63.6	62.6	50.7	25.9		34.8	23.3	11.5	2.7	1.5
30		66.4	66.2	65.2	52.9	28.1		39.4	29.5	14.6	4.2	1.6
							Rural Farm					
15	4.2	7.5	8.2	6.2	4.1	3.4	1.2	2.0	0.5	0.2	0.5	
18	29.5	30.9	35.0	26.4	15.9	11.0	8.8	8.4	2.7	0.8	0.5	0.2
20	39.6	51.7	52.1	38.8	26.3	14.6	13.8	15.2	5.0	2.0	0.7	0.2
25		63.5	61.5	52.2	36.2	19.2		20.3	8.7	3.5	1.5	0.6
30		64.4	62.5	54.6	39.1	22.0		22.4	11.3	5.0	1.5	0.6

SOURCE: Haenszel et al. 1956, Table 17

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TABLE II-9

DIFFERENCES IN SMOKING HABITS BETWEEN WHITE MALE RESIDENTS OF TWO AREAS OF ALLEGHENY COUNTY, PENNSYLVANIA

	Lawrenceville				South Hills			
Age (years) in 1978-79	N	Percent Current Cigarette Smokers	Mean Age at Start of Smoking	Total Tar Intake (g)[1]	N	Percent Current Cigarette Smokers	Mean Age at Start of Smoking	Total Tar Intake
35-44	71	54.9	17.6	-	135	37.0	19.7	-
45-54	79	53.2	16.8	7,570	193	28.5	19.5	5,540
55-64	119	43.7	16.2	-	138	21.7	21.0	-
65+	109	30.3	18.2	10,942	141	18.4	24.8	5,197
All ages	37.8	46.8	17.1	7,529	607	27.1	21.0	5,289

[1] Product of number of cigarettes smoked per day, tar content of cigarette, number of days or years, and number of years since starting smoking. No account may be taken of the amount of the cigarettes smoked or of the depth of inhalation.

-Data not presented

SOURCE: Weinberg et al. 1982

of smoking behavior except the number of cigarettes smoked. Correspondingly, Dean et al. found that the urban/rural risk ratios did not change greatly when these factors were controlled for (independently or together). The data of Haenszel et al. (1956) and Dean et al. (1977, 1978) thus provide strong evidence against Doll and Peto's suggestion that these factors significantly distort urban/rural ratios in cancer rates.

Nevertheless, it would be desirable to calculate the likely contribution of urban/rural differences in age at starting to smoke on the urban/rural differential in lung cancer mortality. However, to do so would necessitate combining data that are not strictly comparable. For a rough theoretical calculation, we use the generalization of Peto (1977) that the incidence of lung cancer is proportional to the 4th power of the duration of exposure to cigarette smoke. Then, for two groups of men who started smoking at ages 17 and 21, and whose smoking habits were otherwise similar, the incidences of lung cancer at age 65 would be in the ratio $(65-17)^4/(65-21)^4$, or 1.416. This figure is consistent with data on U.S. Veterans, summarized by Doll and Peto (1981: Figure E1). Incorporating this ratio into the calculation summarized in Table II-7, we obtain an estimate of 1.48 for the urban/rural ratio that would be expected on the basis of the observed differences in prevalence of smoking in 1955, combined with an assumption that the mean age of starting to smoke was 21 in rural areas and 17 in urban areas, in the absence of urban/rural differences in other risk factors.

Although this calculation involves a number of more or less doubtful assumptions, it suggests that the hypothesized difference in mean age at starting would have to have been much greater than 4 years to account for the observed urban/rural differences in cancer frequency. Although Table II-9 indicates a difference of about 4 years between residents of two districts in one county, Table II-8 does not indicate a systematic difference of even 1 year between urban and rural areas.

The most detailed and comprehensive attempt to control for urban/rural differences in cigarette smoking habits is that of Dean et al. (1977, 1978), already referred to above. The primary objective of the study was to "determine the changes that had occurred in mortality from lung cancer and bronchitis since 1963 and to see how far these were related to changes... in the smoking habits of the population and in air pollution levels." Dean et al. compared data on a sample of 616 males and 150 females who had died from lung cancer in Cleveland County, England, between 1963 and 1972, with data on 2,666 living males and 3,039 living females aged over 35 and interviewed in 1973. Data on the smoking habits and other characteristics of the lung cancer victims were obtained from relatives and from hospital records; data on the living samples were obtained directly by interview. In addition to a number of characteristics of smoking habits, data were obtained on social class, occupation, exposure to dust or fumes, location of residence, and a number of other variables. Data on air pollution were used to classify locations of residence as areas of high, medium, or low pollution even within the areas classified as urban. For analysis, data were stratified by age and various combinations of other variables, and age-adjusted relative risks were calculated by maximum likelihood methods.

The major conclusions of Dean et al. were:

> ...after standardizing for age and smoking habits, and after adjusting for differential population movements in the three pollution zones, male residents living at addresses within Stockton classified as having high smoke and sulphur dioxide pollution had over twice the relative risk of dying of lung cancer as had residents at other addresses. An excess mortality, based on far smaller numbers of deaths, was also found for females.
>
> Secondly, ... only a small part of the marked excess lung cancer mortality rates [among residents of urban areas] would be explained by [smoking patterns] or because they tended to be of lower social class.

Dean et al. attempted to standardize for amount smoked, age at starting smoking, type of cigarettes smoked (plain or filter), and inhalation patterns. They noted some anomalies in relation to age at starting smoking, which they believed may be due to errors in estimating the age at starting smoking by relatives of deceased lung cancer patients who supplied the information. However, they added:

> ...it seems unlikely that, had age of starting to smoke been perfectly accurately assessed in the decedents, it could have explained the urban/rural mortality difference.

The third observation was that:

> ...between 1952/62 and 1963/72, the lung cancer rates of men aged over 55 who were reported never to have smoked increased significantly. This dif-

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ference, about three-fold, could not plausibly be attributed to changes in standards of diagnosis. Equally, it could not be explained in terms of current exposure to pollutants as there has been a downward trend in levels of all the pollutants studied between these two periods. However this difference might be explicable, at least in part, in terms of air pollution if lifetime exposure to pollutants is of importance, as due to the fact that some of the sources of pollution in the area have existed only for 50 years or less, older people in 1963/72 may have had a greater life-time exposure than people of similar age in 1952/62.

...we feel that, taking the facts together in combination it seems reasonable to conclude that air pollution makes a significant contribution towards lung cancer mortality. This conclusion is consistent with the results from Dean's study which showed that, after standardising for age and smoking habits, male inhabitants of Inner Belfast had 3.3 times the lung cancer mortality, and 4.4 times the chronic bronchitis mortality of inhabitants of truly rural areas of Northern Ireland (Wicken 1966).

...smokers of filter cigarettes have a markedly lower relative risk of lung cancer and chronic bronchitis mortality than smokers of plain cigarettes. In view of the national switch towards smoking filter cigarettes, and in view of the reductions in air pollution that have followed the Clean Air Act of 1956, it was to be expected that, in due course, overall mortality from both these causes would decrease if trends in lung cancer mortality rates are studied separately by age-group, the improvements expected from the switch to filters and reduced air pollution can be seen. In 35-39 year old males, for example, national lung cancer rates have dropped 38% between 1956-60 and 1971-75, and increases can now only be seen in men over 70. Male bronchitis rates show an even more marked improvement, with a 30% reduction in overall death rate between 1968 and 1975 and rates declining at all ages except in men 70 or over where they have levelled off (Todd et al. 1976). Lee (1977) has calculated, using Peto's formula... that even in the age groups at which mortality rates are still rising, the rises are markedly less than would have been expected based only on knowledge of distribution of duration of smoking habits, and ignoring the switch to filters and the reduction in air pollution levels. Of course, if standards of diagnosis of lung cancer are still

> improving ...then the benefits of the switch to filters and the reduction in air pollution are even greater than the data suggest.

The major conclusions of the study by Dean et al. (1978) are summarized in Table II-10. After standardizing for age, smoking classification, and age at starting to smoke, urban/rural ratios in lung cancer mortality were 1.50-2.02 for males and 1.46-1.77 for females. Other analyses in the paper by Dean et al. (1978) show that these urban/rural ratios were not strongly affected by differences in the type of cigarette smoked (filter or nonfilter) or by the depth of inhalation, and were not strongly affected by differences in social class. Moreover, there were significant correlations of lung cancer frequency with measured air pollution levels within the urban area.

This study is of particular importance because it controlled simultaneously for so many aspects of cigarette smoking behavior. It has two major limitations. First, although data were collected on occupation and on occupational exposure to dusts and fumes, these factors were not controlled for in the analysis. Standardization for social class probably controlled indirectly for some of the effects of occupational exposure, at least within the urban areas, but a rigorous analysis would be needed to establish this. Second, the data on smoking habits and other characteristics of decedents were collected primarily from surviving relatives, and hence are subject to bias in relation to those collected directly from the living controls. The authors discussed this source of bias and presented evidence

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TABLE II-10

RELATIVE RISK OF MORTALITY FROM LUNG CANCER, STANDARDIZED FOR AGE, SMOKING CLASSIFICATION, AND AGE AT STARTING TO SMOKE, 1963-1972

Area	Males	Females
Eston	2.02	1.77
Stockton	1.50	1.46
Rural districts	1.00	1.00

SOURCE: Dean et al. (1978)

that it was not great. In addition, the bias is likely to have existed in both urban and rural areas, so that the urban/rural ratios may not have been seriously affected.

One study of two geographic areas in Allegheny County, Pennsylvania, which were selected for study on the basis of substantially different lung cancer incidence rates in white males, found that the high risk area had more men who smoked and that these men started smoking at an earlier age (Weinberg et al. 1982; see Table II-8). The authors calculated that the combination of these factors accounted for almost of all of the difference observed between the two areas. Their computations led to the conclusions that 90% of male lung cancers in the "high" area were to be attributed to cigarette smoking. However, they used an unusually high figure for the risks of heavy smokers, which may have inflated this estimate, and they did not take interactions into account. Moreover, several other factors, such as the proportion of industrial workers, and at least one pollution measure--particulate dustfall--showed equally large differences in the same direction as did the cigarette smoking. No correlation was shown with SO_x measures. No comparisons of smoking habits and lung cancer rates were made in women. The smoking data were gathered in a sample survey and did not specifically apply to the men reported to have developed lung cancer in the two areas. As pointed out earlier, the study areas were selected specifically on the basis of an observed large difference in lung cancer rates, so the results cannot be generalized to make inferences about the contribution of smoking to urban/rural or other regional differences in lung cancer rates.

A related study was conducted in Denmark by Broch-Johnsen (1982) in which the author came to the conclusion that "the risk of lung cancer [in Copenhagen] is by 10-40% and 50-140% higher than would be anticipated on account of smoking habits in the youngest (1914-23) and oldest (1894-1903) generations, respectively." While finding that smoking did not account for the urban-rural differences, the author came to the conclusion that "occupational factors are believed to have a greater contribution to the urban factor than diffuse environmental factors... after elimination of smoking". This study is available in English only in abstract form, and a critical review is not possible at this time.

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Doll and Peto (1981: footnote 39) briefly reported unpublished data from their earlier study of mortality in male British doctors (Doll and Peto 1976). Their results are summarized in Table II-11 and show a much smaller urban/rural ratio than other studies that have controlled for smoking habits. However, as Doll and Peto pointed out, all the doctors had been educated in big cities and may have lived as children in areas different from those they inhabited in 1951. The method of standardization for smoking was not stated.

TABLE II-11

LUNG CANCER MORTALITY IN MALE BRITISH DOCTORS,
STANDARDIZED FOR SMOKING AND AGE,
STRATIFIED BY LOCATION OF RESIDENCE

Location of Residence in 1951	Expected Deaths*	Observed Deaths*	Ratio O/E
Conurbations	153.65	152	0.99
Large towns (50,000-100,000)	88.04	94	1.07
Small towns (<50,000)	109.46	108	0.99
Rural areas	78.85	76	0.96

*Period of observation unspecified

SOURCE: Doll and Peto 1981: footnote 39

In each study in which the confounding effects of smoking were controlled, except for that of Doll and Peto (1981), urban residents were found to be at increased risk of cancer even when differences in smoking habits were taken into account. Summarizing these findings and pointing out the interaction effects, Wilson et al. (1980) stated that most of the data

> ...agree that there may be a small increase in lung cancer among [urban] nonsmokers due to air pollution; this is at most half the total incidence among nonsmokers which is already small. The increase of lung cancer among [urban] smokers due to air pollution is 4 times greater than the increase among nonsmokers and is statistically significant.

However, Wilson et al. (1980) did not present a statistical analysis to support the last statement.

The last point made by Wilson et al. (1980), about the greater association with air pollution in smokers, is of particular importance. The results of Haenszel et al. (1962), Dean (1966), Dean et al. (1978) and Cederlof et al. (1975) indicate that cigarette smoking and air pollution probably interact synergistically. A possible mechanism for this apparent synergism was demonstrated by Cohen et al. (1979), who found that smoking inhibits the action of cilia in long-term dust clearance from the lungs.

Interactions between smoking and air pollution would account for some of the differences between men and women in patterns of lung cancer. If interactions of this nature did occur, then we should expect that larger urban/rural differences would be seen for males, who smoke more than women and who generally started smoking earlier. This has been observed in several studies (see Tables II-2, II-3, II-4, II-5, and II-10). Similarly,

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if such interactions did occur, urban/rural differences for female smokers should be larger than those for female nonsmokers.

The increase in the urban/rural difference among women smokers (relative to nonsmokers) expected on the basis of an assumption of interaction, however, has not been consistently observed. Haenszel and Taeuber (1964) reasoned that this may be due to the relatively small proportion of female smokers before the 1950's (this leads to large sampling variation in estimated risks and slopes of the smoking class gradient). They also noted that the problem of small numbers of women smokers is compounded by the smaller "effective" exposures among women smokers relative to their male counterparts (i.e., women don't inhale as deeply as men and tend to smoke low-tar cigarettes and cigarettes with with less tobacco). The other studies in which women's smoking habits were recorded (Dean 1966, Dean et al. 1978, Hitosugi 1968, and Cederlof et al. 1975) suffer from similar problems. Of these studies, only the results of Cederlof et al. (1975) are consistent with an interaction effect among women.

b. Occupational exposure

Several investigators have also postulated that much of the urban excess of lung cancer can be accounted for by exposure to carcinogens in the work place. In some situations, studies have provided support for this hypothesis. For example, an excess of lung cancer deaths was observed among white males in south central Los Angeles County during the years 1968-1972

(Menck et al. 1974). Lack of a clear basis for smoking or occupational factors to explain the excess led the authors to conclude that ambient air pollution was the causative factor. A later case-control study was undertaken (Pike et al. 1979) and it was concluded that increased risks associated with occupation could account completely for the observed excess.

However, Pike et al. (1979) in fact found associations between lung cancer and both smoking and occupational categories; on the basis of these associations, they calculated that the differences in smoking habits and occupations between the areas of Los Angeles County originally studied by Menck et al. (1974) would account for a relative risk of 1.26. This is smaller than the relative risk of 1.40 originally observed by Menck et al. (1974). Hence, there is still a portion of this difference that is unexplained by smoking and occupation. The sensitivity of both studies was limited by the observation of Pike et al. (1979) that most of the cases had migrated into the area during the preceding 20-40 years.

The data of Hammond and Garfinkel (1980) also suggested that occupational exposure may account for part of the urban excess. The excess of lung cancer deaths in urban and rural areas in their study was reduced when occupational exposure (defined in the study questionnaire as exposure to dust, fumes, gases, or X-rays) was taken into account. This reduction was evident in almost every residence category. This definition of occupational exposure is not precise, of course. The study population was composed of a larger proportion of whites, white-collar workers, and better educated individuals than the U.S. population as a whole, which could lead to an underestimate of the effects of both air pollution and occupational exposure. When lung cancer mortality versus location of residence is plotted separately for occupationally exposed and nonoccupationally exposed men, separate effects of both occupation and residence are apparent (see Figure II-2). Hammond and Garfinkel reported that these data were corrected for cigarette smoking.

Doll and Peto (1981) provided a quantitative interpretation of these data, noting that after standardizing for smoking, the mortality from lung cancer was only 14% greater in men who gave a history of exposure to dust, fumes or mists (including asbestos) than in men who did not. Since only 38% of lung cancer deaths occurred in men who gave a positive history of occupational exposures, Doll and Peto calculated that the total contribution of these factors to the production of lung cancer in the ACS population appears to have been 4.6%. However, Doll and Peto pointed out three ways in which an estimate of this kind could be too low: the diluting effect of random errors, the possibility that the ACS population was biased by the inclusion of proportionately few blue-collar workers, and the possibility that undiscovered carcinogenic risks may occur in industries in which there are no recognized dust, mists, or fumes. Doll and Peto proposed (on the basis of admittedly subjective and "stop-gap" methods of estimation) that

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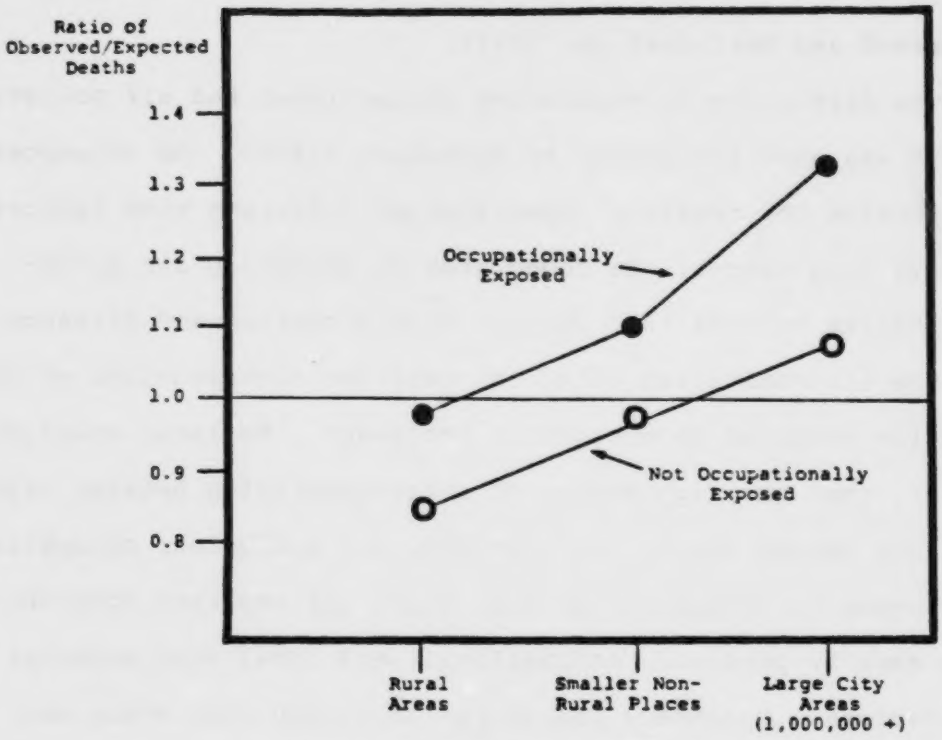
FIGURE II-2

RATIO OF OBSERVED/EXPECTED LUNG CANCER DEATHS IN MEN BY RESIDENCE AND OCCUPATIONAL EXPOSURE, 1959-1965[a]



[a]Adjusted for age and smoking

SOURCE: Hammond and Garfinkel (1980), Goldsmith (1980).

the fraction of lung cancer deaths ascribable to occupational hazards in the U.S. in 1978 was about 15% in males and 5% in females. At least in males, this fraction included some cases also ascribed to cigarette smoking. However, Doll and Peto did not discuss possible interactions with air pollution, and did not discuss or estimate the contribution of occupational factors to the urban/rural ratio, except to quote the opinion of Hammond and Garfinkel (p. 1247).

The difficulty in separating occupational and air pollution factors was also recognized by Greenberg (1979). He attempted to determine the relative importance of different risk factors for male lung cancer. He found that by adjusting air pollution indices to take into account wind direction and distance from the air monitoring site, the relative contributions of air pollution compared to occupation increased. He later concluded, however, that the high degree of intercorrelation between high-risk lung cancer indicators (smoking, air pollution, occupation, etc.) makes it infeasible to pull apart the separate contributions made by personal, occupational, and local environmental risk factors. Greenberg considered it likely that there are interactions between air pollution, occupation, and smoking.

In a case-control study of white male lung cancer patients from Erie County, New York, from 1957 to 1965, Vena (1982) was able to study the effects of age, smoking, occupation, and air pollution and their combinations. Air pollution was stratified into pollution zones by means of air sampling data for particulates collected from 1961 to 1963 and by an historical review of point sources. Exposure to air pollution was indexed by the number of years of residence in a zone of high or medium air pollution. Occupational exposure was defined as the number of years in a job category with potential exposure to respiratory carcinogens or with documented elevations in risk for lung cancer. Smoking was defined in terms of years smoked, weighted by four categories for amount smoked (less than 0.5 pack/day; 0.5-1 pack per day; 1-2 packs/day; and 2 or more packs per day). Data on age at starting, type of cigarettes and degree of inhalation were not available. Although misclassification may have occurred and smoking may still be a confounding factor, this study by Vena (1982) is among the most detailed available, especially in that the simultaneous influences of smoking, occupation, and smoking were assessed.

When exposure to air pollution was defined as exposure to high or medium pollution for 50 or more years, occupation as exposure in high risk jobs for 20 or more years, and smoking as exposure for 40 or more pack years, it was evident that occupation and probably air pollution interact with cigarette smoking to modify its effect. Significant ($p<0.05$) age-adjusted relative risks were observed for smoking (RR=3.30) air pollution and smoking (RR=4.73), occupation and smoking (RR=6.37), and all three combined (RR=5.71). When the data were stratified by age to separate those born after the turn of the century from those born before, the under 60 years of age category showed significant associations between cancer risk and each of the three individual variables (smoking, occupation and air pollution) and each of the combinations between variables. The over 60 years of age category paralleled the associations observed for the overall, age-adjusted relative risks.

When Vena (1982) adjusted the relative risks for age, occupation, and smoking, he observed a small (and nonsignificant) unexplained lung cancer risk for the medium or high air pollution areas (compared to the low pollution areas) of 1.03 for residence of 30 to 49 years and 1.26 for residence of more than 50 years. Vena (1982) cautiously interpreted this study as indicating that air pollution should not be dismissed as a risk factor in lung cancer because of the apparent synergism of air pollution with smoking and with the combination of smoking and occupation. He concluded, however, that his findings do not support the hypothesis that air pollution alone significantly increases the risk for lung cancer.

Other investigators have reported their belief that occupation is not a major factor contributing to the urban excess. Doll (1978) stated that occupational hazards were "...unlikely to be a major factor as the known and suspected hazards...affect only a small proportion of the total urban population." As mentioned earlier, Blot et al. (1977) made much the same point, noting that, if the higher cancer rates in petroleum counties were the result of occupational exposure, the relative risk to these workers would have to be substantially higher than the general population, but this has not generally been observed.

c. Migration

Concerns have been raised that migration can have the effect of increasing the apparent geographic variability because: (1) it may produce areas in which the age distribution of the population differs considerably from the U.S. average, and (2) persons who migrate are likely to have a different health status from that of those who remain behind.

Mancuso (1976) reported that much of the differences in lung cancer mortality rates that he found in Ohio came about as a result of the very high rates observed in migrants to Ohio from the rural areas of the southeast United States. Blot and Fraumeni (1981) have recently reported that the lung cancer mortality rates in the southeast now exceed those of the northeast and Great Lakes states. Mancuso interpreted his findings to imply that a prior initiating exposure was more likely to have occurred to the migrants (in contrast to sedents) and that later, promoting exposure then had a greater effect on migrants than on life-long residents.

The first problem can be avoided when enough data are available to calculate age-specific and age-adjusted mortality rates. In the studies based on the mortality data for U.S. counties compiled by the National Cancer Institute (e.g., Blot and Fraumeni 1976), appropriate standardization has already been performed.

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The second problem, the possibility of selective migration into or out of an area, might be corrected for if detailed statistics were available on duration of residence. By studying only those individuals who have remained in an area for 20-30 years a more accurate assessment of environmental effects could be obtained. In most studies of urban/rural differences, such data are generally not available. It is possible that a small percentage of the urban/rural difference might be due to the migration of chronically ill persons to areas (generally urban) with better medical facilities, or migration of healthy individuals out of these urban areas. Migration between geographic areas, however, generally is expected to reduce the sensitivity of geographical studies as the distinction between exposed and unexposed is gradually lost. As such, the statistical power of such studies might be grossly overestimated if migration were not taken into account. The longer the latency period of disease, the larger this dampening effect of migration is likely to be.

As noted earlier, Polissar (1980) has estimated that 40-50% of the relative excess risk is not reflected in the estimated risk for most cancers when rates are compared between exposed and unexposed counties and migration has taken place during a 30-year latency period. This finding is consistent with the results reported by Haenszel et al. (1962), who found that the urban/rural gradient for the standardized lung cancer mortality ratios (adjusted for age and smoking) increased with

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the duration of residence. The role of urban air pollution in explaining this trend, however, is unclear because the SMR for urban residents declined with duration of residence, possibly reflecting improved survival patterns of the less exposed persons, or the initiation--promotion phenomenon suggested by Mancuso.

d. Population density and other factors

Demopoulos and Gutman (1980) labeled a series of cities as "clean" and "dirty," based on a qualitative characterization of the nature of the local industries but not on direct measures of the nature or intensity of ambient air pollution. They concluded that when areas with comparable population densities were compared, general air pollution (i.e., in "dirty" cities) and workplace exposure (in regions of heavy industry) were not associated with cancer risks. This conclusion led them to the speculation that much of the urban excess might be due to higher population density. However, their designations of "clean" and "dirty" cities were not related to any measured distinctions between areas of low and high air pollution. Their presumption that heavy industries should be more likely to be associated with cancer risks than light industries may not be true. Major carcinogenic hazards have been recognized in a number of light and service industries. Thus their characterization of "clean" and "dirty" cities is unsatisfactory even as a surrogate measure of either air pollution or of occupational exposure. Among other problems with this study, no attempt was made to standardize for smoking or other risk factors, and the basis for selecting the sample of cities was unclear.

Population density is strongly correlated with a number of other factors and may represent a proxy measure of air pollution and a variety of other variables. In studying the relationships between population density, vehicle density (as an indicator of motor vehicle emissions), and total cancer mortality, Robertson (1980) concluded that vehicle density rather than some other correlate of population density is associated most strongly with cancer mortality. Vehicle density, of course, implies air pollution from burning fossil fuels in mobile sources. Robertson found that the number of motor vehicles per square mile does not increase linearly with population density, but levels off in the more densely populated cities where public transportation is often more readily available. He reported that cancer rates do not increase linearly with city size but do appear to be linearly correlated with motor vehicle density. Robertson (1980) concluded that "motor vehicles appear to be a substantial part of the 'urban factor' in cancer." However, he failed to control for potential differences in several other important factors (such as smoking, occupation, and migration). Currently available data are insufficient to estimate the relative contributions of mobile sources and stationary sources of air pollution. It is likely that in some areas the largest source of conventional air pollutants is the automobile (e.g., Los Angeles) while in others, industrial sources are more portant (e.g., Charleston, West Virginia). In their recent review, Wilson et al. (1980) came to much the same conclusion. However, the relative contribution of mobile and stationary sources to atmospheric concentrations of carcinogenic air pollutants is not known.

In studies where attempts have been made to control for population density and other confounding factors, the correlation between such variables as air pollution and population density may seriously distort the estimated effects of air pollution. There is some evidence that the onset of population-wide cigarette smoking paralleled industrialization. If that were the case, regression analyses that attempt to estimate effects of air pollution may be distorted by controlling for factors that are correlated with air pollution. Air pollution has also been found to be inversely related to socioeconomic status (SES) (Bozzo et al. 1979, Lave and Seskin 1977). Since low SES groups (who are usually heavier smokers) are exposed to higher pollution levels than high SES groups, the true effects of air pollution are likely to be underestimated by controlling for effects of SES and/or smoking.

F. Summary

This chapter summarizes epidemiological studies of cancers in the human population and their relation to air pollution and other factors. Section II.B introduces the four principal types of epidemiological study and discusses issues that arise in applying them to the cancer/air pollution problem. Although

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there is evidence that air pollutants may affect cancers at a number of anatomic sites, only lung cancers have been studied in sufficient detail for critical analysis. Air pollution is a complex mixture of agents, and most available measurements are of conventional pollutants which are unlikely to be carcinogenic in themselves; furthermore, the use of a single component, such as benzo[a]pyrene, as a surrogate measure of the carcinogenic potential of polluted air may not be entirely satisfactory. Significant exposure to some air pollutants occurs in indoor environments, where monitoring data are scanty. The long latent periods for human cancers mean that current cancers should be associated with exposures in past decades, when some pollutants were present at higher levels and others at lower levels. The most pervasive difficulty encountered in the conduct and interpretation of epidemiological studies is the control of confounding factors, especially cigarette smoking. Other problems that arise include the interpretation of sex and racial differences in patterns of cancer mortality, the insensitivity of many studies, and the selection of appropriate comparison populations.

Section II.C summarizes source-specific or "neighborhood" studies. A number of studies have reported apparent elevations in cancer rates in the vicinity of industrial facilities of various types. Some of these studies were of the large-scale "ecologic" type, whose results are usually regarded as no more than suggestive. Most other studies in this category had substantial limitations, including problems in identifying appropriate control populations, in controlling for smoking, occupation, and demographic factors, and in verifying exposure. The more persuasive evidence of this kind is the finding of rare types of cancer characteristic of exposure to vinyl chloride and asbestos near putative sources of these materials, and the statistical association in several studies between lung cancer rates and proximity to smelters and other facilities handling arsenic compounds.

Section II.D summarizes several studies that suggest that migrants from one country to another with higher (or lower) air pollution levels continue to experience cancer rates characteristic of their native countries. However, the rigor of the statistical comparisons of cancer rates is questionable, and the differences were not related to specific data on exposure to air pollution.

Section II.E summarizes urban-rural and other geographical studies. Table II-1 (Appendix A) tabulates 44 epidemiological studies of cancers of the lung and other sites in human populations. In 25 of these studies, a statistical association was reported between cancer rates and one or more (direct or indirect) measures of air pollution, and most of the rest reported excess frequencies of cancer in urban areas relative to rural areas. Only five studies reported finding no association between cancer rates and either urban location or measures of air pollution. However, all the studies were subject to various limitations, which complicate their interpretation.

The most pervasive and difficult problem in these studies is control for the confounding effects of cigarette smoking. Ten studies of lung cancer rates in nonsmokers have shown rather consistent urban-rural differentials in males, but not in females. However, all but one of these studies were limited by small sample size, and none was controlled for occupational exposures. In a number of studies, urban/rural differentials and statistical associations between cancer rates and air pollution remained significant after attempts were made to control for the effects of smoking, using data on smoking habits in cancer victims or population groups. However, the completeness of the control for smoking in these studies is disputed. Some scientists have argued that differences in aspects of smoking such as age at starting to smoke and depth of inhalation cannot be controlled for. However, actual data on these aspects of smoking do not confirm that they would contribute significantly to urban/rural differentials.

Only a few studies have been controlled for the effects of occupational exposures. One study that was so controlled revealed significant urban/rural differentials in both occupationally exposed and unexposed groups, after controlling for smoking. Other studies have suggested interactions between effects of occupation and air pollution.

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III. EXPERIMENTAL EVIDENCE AND MONITORING DATA

A. Introduction

This chapter reviews and summarizes the evidence that air contains substances capable of causing or contributing to the incidence of cancer in humans. Monitoring studies have shown that air contains substances known on the basis of human and animal studies to cause cancer. In addition, extracts of air pollution particulates have been shown to be both mutagenic and carcinogenic in laboratory studies.

Air pollutants arise from both anthropogenic and natural sources, such as vegetation, weathering, and fires. Air pollutants of anthropogenic origin can be placed in three broad categories: vapor-phase organic chemicals, such as volatile emissions from industrial processes; particulate organic matter, which includes products of fossil fuel combustion and vehicle emissions; and inorganic substances, such as compounds of the metals lead, nickel, and arsenic, and the mineral asbestos. The amount of vapor-phase organics emitted in the United States has been estimated to be 1.9×10^{13} g/yr, with particulate organics being one-fiftieth to one-tenth of this amount (Hughes et al. 1980, citing Duce 1978). Estimates of the amount of anthropogenic inorganic pollutants are difficult to make, because of the wide variety of possible sources and the large contribution of natural sources to the levels found in ambient air. Of the three categories of pollutants, however, the particulate fraction of air pollution has been subjected to the most investigation and is of most concern for long-term human health effects. This concern stems from the known biological activity of many of the constituents of particulate matter, such as the polycylic aromatic hydrocarbons (PAHs), and because particulate matter occurs at high local concentrations around sources in populated areas.

A sample of polluted air is a complex and dynamic mixture that can contain over 300 compounds. It can consist of chemicals in the vapor or gaseous phase, relatively pure aerosols or particulates of specific substances, or heterogenous particular aggregates of many substances. The relative distribution of chemicals between the vapor and particulate phases is highly dependent upon their source, their vapor pressure and polarity, and the ambient air temperature. Although particulate matter may be thought of as a collection of solid or liquid particles, vapor-phase organics may be adsorbed under a range of conditions into the particulate content of polluted air, changing their chemical composition (Hughes et al. 1980). In addition, air pollutants, especially reactive species such as NO_X and ozone, itself derived from precursor pollutants, can undergo photochemical or spontaneous reactions to produce new compounds that may have more or less biological activity than their precursors. All these factors complicate the identification of the components of polluted air and their relation to the biological activity that is measured by in vivo or in vitro studies.

An additional consideration in reviewing the experimental evidence associating air pollution and cancer is the difficulty in determining the substances and the levels to which people are actually exposed. This difficulty stems, first, from problems in sampling air for pollutants, and second, from the complicated and largely uninvestigated processes through which inhaled materials affect humans. One of the problems in sampling is that, although some monitoring stations can sample air continuously over long periods of time, most samples are limited in the period of time over which they are obtained and therefore may not represent all the pollutants in an area that result from changing weather conditions and pollution sources. Also, sampling is usually performed at roof level or close to a known source of emissions; neither accurately reflects the air quality at street level that most people experience. Although advances have been made in the design of personal sampling devices to provide more accurate samples of the air that people breathe, most of the studies of the biological activity of air pollution and its chemical characterization have used samples that were limited in both time and location and therefore may not be representative of the actual toxicity and content of ambient air. In addition, determination of the effect of airborne substances on human health must consider the physiological processes that take place between the inhalation of a substance and the ultimate site of its toxic effect. The effect of an inhaled carcinogen depends on its distribution in the lungs, its retention and absorption, possible metabolism by lung tissue, its distribution via the circulation, and the concurrent presence of irritating substances. Some studies have investigated these factors and are discussed below.

B. Experimental Evidence

Experimental evidence for the presence of carcinogens in ambient air has been provided by both *in vivo* and *in vitro* testing of extracts of airborne material. This testing, however, has been limited to particulate material. Because of the volatility, relatively low concentrations, and rapid degradation of vapor-phase organic substances, no methods are currently available for collecting of these chemicals from ambient air and testing them *in vivo* or *in vitro*. The carcinogenicity of these substances can be assessed by testing them in pure form at high concentrations, and this type of evidence is discussed in the section on monitoring data. The basic approach to determining the biological activity of airborne particulate matter is to collect on filters the particulates that are suspended in the air or released from an emission source, extract this material with organic solvents, and apply the extract to the test system.

The composition of these extracts depends on the chemical and physical nature of the original particulates--specifically, whether they were homogeneous, aggregates, or contained adsorbed organic chemicals--and on the ability of the fractionation and extraction system to solubilize the chemicals that are present.

Because of this approach and the dilute nature of air pollution, the quantity of material available for testing is usually limited. Researchers have worked around this problem by either making extracts of more readily available material, such as soot and tar that condense from combustion emissions, or by using a small number of animals in assay systems that are sensitive to carcinogens. These systems include the painting of test material on the skin of mice, injection into neonatal mice, and instillation into the lungs of hamsters and rats. Alternatively, researchers have tested extracts in cell cultures that are capable of detecting chemicals that cause mutations or cell transformation although they do not directly measure carcinogenic activity. Both phenonomena are considered predictors of carcinogenic potential.

1. In Vivo Tests of Extracts of Air Pollution for Carcinogenicity

As mentioned above, the dilute nature of air pollution limits the amount of material available for *in vivo* testing. In the earliest studies, investigators prepared extracts of soot, coal tar (a condensate resulting from the combustion of coal under low oxygen conditions), and particulate matter and applied them repeatedly to the skin of mice. In a review of these studies, Shabad (1960) cited several investigations in which skin tumors and adenomas of the lung were induced by extracts of coal tar. Also, when dichloroethane extracts of soot were painted on mice three times weekly, papillomas (benign skin tumors) appeared after 10 weeks, metastasizing in 37% of the animals to sites in the lungs and lymph nodes (Shabad 1960). Shabad also reported that extracts made from airborne particulates induced malignant tumors in 8% of the test animals when the same protocol was used.

In another dermal application study, Hoffman (1964) applied to the skin of female mice an acetone solution that contained 12.5% organic matter from an extract of polluted air that was measured as having 20 μg of organic material per m^3. After 9 months, 23 of the 30 mice had developed multiple papillomas, and 10 had carcinomas; after 3 more months of treatment, a total of 19 of the mice had malignant tumors. Animals in a group that were being concurrently treated with a solution of a mixture of PAHs at a concentration equal to that of the air extract had 4 tumors, half of which were malignant. Another group painted with an equivalent amount of BaP did not develop any tumors.

Gasoline engine condensate (GEC) and diesel exhaust condensate (DEC) were examined for carcinogenicity in a skin-painting study with female CFLP-mice (Misfeld 1980). In addition to these materials, BaP and a mixture of 15 PAHs at the same proportions as found in GEC were tested. Each material was tested at three concentrations in 80 mice per concentration. GEC, DEC, BaP, and the PAH mixtures all gave positive responses with positive dose-response relationships. The largest response given by GEC was 83% in the high concentration group. DEC gave a high response of 13%. It was calculated that GEC was 42 times as potent as DEC, and the PAH mixture only accounted for 41% of the GEC activity. Calculations indicated that BaP contributed 9.6% and 16.7% of the activity found in GEC and DEC, respectively.

Most recently, Nesnow et al. (1982) investigated the tumor-initiating and tumor-promoting abilities of extracts of emissions from automobiles with gasoline and diesel engines, from a coke oven, from roofing tar, and from a residential furnace that burned diesel fuel. The animals used were Sencar mice, which have been bred for their sensitivity to dermally applied carcinogens and are widely used in studies of the mechanism of carcinogenesis. The collected emissions were extracted with dichloromethane, which was removed by evaporation, and the resulting material was applied as a solution in acetone in one or more of four protocols in doses ranging from 100 to 10,000 μg/mouse. Under the tumor initiation protocol, each dose was applied once topically, followed after 1 week by twice weekly applications of the tumor promotor, tetradecanoylphorbol-13-acetate (TPA). To determine the ability of the extracts to act as complete carcinogens, samples were administered weekly for 50 weeks. Under the tumor promotion protocol, the mice were treated with one dose of BaP and then weekly for 34 weeks with the sample. To test for cocarcinogenic activity, both the test material and BaP were applied initially, followed by TPA twice weekly.

These studies indicated that BaP and extracts from emissions of coke ovens, roofing tar, and one type of diesel-powered automobile were potent initiating agents. The emissions from the other diesel automobiles and the gasoline engine automobile showed some initiating activity. BaP, coke oven emissions, and roofing tar emissions were also shown to be complete carcinogens. None of the diesel emissions from the automobiles or furnace gave positive results in the complete carcinogenesis assay; the authors hypothesized that this result may have been due to the cytotoxic effect of these extracts when applied chronically. BaP and coke oven and roofing tar emissions also showed tumor-promoting ability; none of the diesel extracts was tested in this protocol. Because of the positive results for BaP in all the protocols, the authors considered that the activity of the emissions extracts may have been due to their BaP content. However, analysis of the samples for BaP and comparison of these values to tumor-initiating ability indicated that the BaP content did not account for all the activity of the extracts.

Depass et al. (1982) have also recently reported results of their skin-painting study. In this study, the initiating, promoting, and complete carcinogenic activity of diesel exhaust particulate (DP) and dichloromethane extracts of diesel exhaust particulates (DCM) were examined using C3H strain mice. The study was to end with the death of all mice, but the reported interim results covered 714 days of treatment with mice still living in most groups. The mice were treated with two concentrations of DP and four concentrations of DCM for the complete carcinogenesis study, one concentration of DP and two concentrations of DCM for the promotion study, and one concentration of each for the initiation study. Along with the specific control groups, there was a total of 18 different groups consisting of 40 mice each.

In the study on complete carcinogenesis of DP and DCM, only one tumor was found in a treated mouse. This mouse was in the high-dose DCM group. Slight response was also seen in the promotion study; one animal in each DCM dose group had a squamous cell carcinoma, and a second low-dose DCM animal had a papilloma. Three mice in the DP and DCM groups had tumors in the initiation study. Tumors, however, were found in one acetone-initiated control group mouse and two phorbol 12-myristate 13-acetate (PMA) initiated control group mice. PMA was used as a promoting agent for the promotion study. The difference in response between the studies of Depass et al. (1982) and Nesnow et al. (1982) may have resulted from a difference in the source of test substances, a difference in mouse strain or sex, or a difference in treatment regimen.

Extracts of polluted air have also been administered to test animals by subcutaneous injection. Hueper et al. (1962) prepared benzene extracts of city air, concentrated them by evaporation, and injected 1% (w/v) solutions into C3H or C57 mice monthly for periods of up to 2 years. This treatment induced local tumors in 2-18% of the animals, the latency period being from 9 to 24 months. These results were, however, distorted by substantial mortality in the test group because of the toxicity of the extracts. Epstein et al. (1966) developed a more sensitive assay, giving neonatal mice one to three injections of the test material during the 1st week of life and sacrificing the animals up to 1 year later. Extracts of air particulates still caused mortality in the test group, but the survivors developed hepatomas, lymphomas, and solitary and multiple pulmonary adenomas at rates significantly greater than those for the control group.

In a later study, Rigdon and Neal (1971) collected air pollutants in the vicinity of petrochemical plants, made benzene extracts, and injected these once into 30- to 50-day-old CFW mice. They observed the animals for up to 1 year, noting when tumors appeared. The treatment induced as much as a 60% incidence of local, nonmetastatic fibrosarcomas. This rate was greater than that resulting from the injection of mice with an amount of BaP equal to that in the extracts. This suggested to the authors that multiple carcinogens or cocarcinogens were present in the extracts.

Asahina et al. (1972) used Epstein's neonatal mouse assay to test 10 fractions of an extract of New York City air. Significant increases in the number of tumors, including pulmonary adenomas and lymphomas, were found for four of the fractions. More recently, Epstein et al. (1979) reported a dose-response relationship between total tumor incidence and the cumulative total dosage of the extracts injected into mice. The extracts, which were found to contain PAHs, quinolines, and acridines, induced solitary and multiple pulmonary adenomas and lymphomas in both sexes and hepatocellular carcinomas in males.

More recently, Pott et al. (1980) collected airborne particulate matter from urban and rural locations, prepared organic solvent extracts, and analyzed fractionated extracts for BaP and other PAHs. The extracts were then injected subcutaneously and chronically into mice in a range of doses based on BaP content. Extracts with BaP contents of 0.37-1.1 µg induced tumors at rates up to 30%, and a dose-response relationship was seen with the fractions that predominantly contained PAHs. Other fractions, containing primarily polar substances, had some carcinogenic activity.

A few investigations have been performed to test the capacity of fractions of polluted air to induce cancer in lung tissue. In these experiments, the test material was instilled into the trachea of anesthetized animals from which it is easily distributed into the lung. Bogovski et al. (1970) reported that a benzene extract of oil shale soot containing 0.01% BaP induced lung cancer in rats after this type of intratracheal instillation. Mohr (1976) instilled a condensate of automobile exhaust into the trachea of hamsters at 2-week intervals for 30 or 60 weeks. The condensate, which contained a small amount of BaP (1.7 µg/animal), induced pulmonary adenomas in all the hamsters, a response the author could not attribute to the BaP content alone. In a similar study, Kommineni and Coffin (1976) applied a gelatin suspension of air particulates, BaP, or particulates and BaP to the trachea of hamsters once a week for 8 weeks. All three groups showed progressive and severe inflammatory changes in the lungs; the third group, which was treated with the particulates and BaP, showed evidence of the formation of bronchial polyps. In addition to these studies, researchers at the Health Effects Research Laboratory of the U.S. Environmental Protection Agency are completing studies of the effects of the long-term inhalation of diesel exhaust in mice and hamsters (Pepelko 1980).

The studies of the biological activity of extracts of air pollution in animals do not provide data that are directly applicable to predicting health effects in humans. Differences in the routes of exposure and the use of high concentrations limit the extent to which the results may be extrapolated to human exposures, while the toxic, noncarcinogenic, effects of the extracts limit the sensitivity of the tests to detect carcinogenesis. In summary, however, they do indicate that ambient air, or materials released into air, contain compounds that by themselves or acting together have the ability to induce cancer in mammals.

2. In Vivo Studies of Irritant Effects of Particulates

The ultimate effect of an inhaled carcinogen, which may be in the form of particles or adsorbed on particulate material, depends on several interrelated factors: the distribution of the carcinogen in the lungs, its retention and absorption, and the concurrent presence of respiratory irritants.

The size of a particle determines the extent to which it penetrates the respiratory tract. In nasal breathers, particles from 12.5 nm to 2.5 μm in diameter are capable of penetration of the alveolar region of the lungs. Particles greater than 2.5 μm in diameter are mostly removed in the nasal chambers, and those less than 12.5 nm remain suspended in tidal air and are exhaled (Kotin 1968, Shannon et al. 1974). Studies have also shown that retention of particulate matter in the lungs is greatest at 1.0 μm in diameter and falls off sharply for sizes greater than 2 μm or less than 0.25 μm (Kotin and Falk 1963). For mouth breathing the size of particles deposited in the alveolar region of the respiratory tract can be up to 10 μm. In addition, particles up to 15 μm may be deposited in the tracheobronchial portion of the respiratory tract. Clearance of very large particles in the alveolar region is slower than for smaller particles (USEPA 1982). Polluted urban air contains particles in the range of 12.5 nm-2.5 μm; particles of this size are also produced by the burning of solid fuels and are present in the exhaust of gasoline and diesel engines. Particle size may also influence the rate and extent of elution of carcinogenic chemicals from the particles on which they are adsorbed. Falk and Kotin (1962) found that the lower size limit for PAH release from particles in physiological conditions in vitro was 100 nm in diameter. Therefore, particles from 100 nm to 10 μm in diameter are probably of the greatest biological significance, because they can readily penetrate and be retained in the respiratory tract and adsorbed carcinogenic substances can be released.

The role of the penetration and retention of particles in the lungs in inducing cancer has been investigated in a number of studies. Inhaled ferric oxide (Fe_2O_3) dust is an example of particulate material that, although not carcinogenic to laboratory animals by itself (Gilman 1962), enhances the effects of known carcinogens. This observation was initially made by Saffiotti et al. (1968, 1972a,b) in studies in which ferric oxide particles and various carcinogens were concurrently instilled into the tracheas of hamsters.

Feron et al. (1972) showed that the tumorigenic effect of diethylnitrosamine in the hamster respiratory tract was increased by a factor of 3 when instilled in hamsters with ferric oxide particles in solution. This enhancing action of the ferric oxide particles has been attributed to their ability to increase the penetration and retention of carcinogenic substances that are bound to them. This possibility was investigated by Sellakumar et al. (1973), who reported that adhesion of fine particles of BaP to equal-sized particles of ferric oxide was critical for tumor induction by intratracheal instillation. Without the physical adhesion to the ferric oxide dust, much higher doses of BaP were needed to induce tumors in hamsters.

Henry et al. (1975) confirmed these results and, by microscopic comparison of the lungs from the hamsters treated with ferric oxide particles coated with BaP to the lungs of those administered a mixture of the dust and the carcinogen, determined that the particles of the mixture were removed from the lungs more rapidly. However, other studies have shown that the ability of injections of the carcinogen diethylnitrosamine to induce lung tumors in hamsters was increased by the tracheal instillation of ferric oxide particles (Montesano et al. 1970, Nettesheim et al. 1975). These results suggest that the particles may have a tumor-promoting effect in addition to enhancing carcinogen penetration and retention.

In addition to ferric oxide, other particulates have been shown to enhance the action of carcinogens. Studies have shown this effect with BaP and particles of asbestos (Miller et al. 1965, Pylev and Shabad 1972), titanium oxide, aluminum oxide, carbon (Stenback et al. 1976), and india ink (Pylev 1963). The mechanism of these actions is unknown; Lakowicz and Hylden (1978) demonstrated, however, that asbestos fibers increase the lipid solubility of BaP, and hence could increase its cellular uptake.

Respiratory irritants present in polluted air also may increase the carcinogenic effect of airborne substances by changing the function and structure of the respiratory epithelium and increasing their retention. These irritants interfere with ciliary activity and with the flow of the mucous stream. Air pollutants that act as irritants to the lining of the respiratory tract include sulfur oxides, nitrogen oxides, ozone, chlorine, ammonia, pollen, and allergens (Kotin 1968). Laskin et al. (1970) demonstrated in rats that simultaneous inhalation of the respiratory irritant sulfur dioxide and the carcinogen BaP resulted in the production of squamous cell carcinomas of the lung. Experiments performed by Richters et al. (1979) suggested that exposure to respiratory irritants also increased metastasis to the lung. The authors injected melanoma cells, which readily metastasize to the lung, into mice that had been exposed for 10 weeks to an atmosphere containing nitrogen dioxide at 0.4 ppm. At 10 and 21 days after infusion, the exposed animals showed significantly more melanoma nodules in the lungs than did the controls, which had breathed filtered air.

3. In Vivo Mutagenicity and Genotoxicity Testing

The mutagenicity and genotoxicity of air pollutants, most notably diesel exhaust, have been studied in several animal models. These *in vivo* tests are usually short term, and their use of the whole animal is an obvious advantage over *in vitro* assay systems. In addition, the test compound may be administered by appropriate routes. These *in vivo* assays, however, usually are less sensitive and quantitative than *in vitro* assays where the cells come into direct contact with known amounts of test compound.

In a series of genotoxicity studies on diesel and gasoline exhaust, as well as coke oven and roofing tar emission, several investigators used a variety of in vivo tests, which included the sex-linked recessive lethal test on *Drosophila melanogaster*, metaphase analysis, micronuclei assay, sperm morphology assay, sister chromatid exchange assay, chromosomal abnormalities assay, and a liver foci assay.

Schuler and Niemer (1980) examined the effect of exposure to Nissan diesel engine exhaust gases in producing sex-linked recessive mutatations in Drosophila melanogaster. The flies were exposed to a five-fold dilution of exhaust gases for 8 hours. The exposed male Oregon-R strain flies were mated with Muller-5 strain females. Two broods of the F_2 generation and one F_3 generation brood were examined for sex-linked recessive mutation. No mutagenic activity was observed. The authors pointed out that a more thorough assessment would necessitate testing at higher exposure doses.

Pereira et al. (1980a) examined the genotoxicity of diesel engine exhaust in female Swiss mice using metaphase analysis and a micronuclei assay. The mice were exposed for 8 hours per day, 5 days per week, for 1, 3, and 7 weeks. The exhaust was diluted 18-fold and contained a final particulate concentration of 6-7 mg/m^3. Bone marrow cells were used for the metaphase analysis, which involved examination of cells in metaphase. This assay can identify compounds capable of breaking chromosomes and chromatids. Only the animals exposed for 7 weeks were examined, and no effects were observed. The micronuclei assay was done on animals at all three exposure periods. Polychromatic erythrocytes in bone marrow were examined. This assay can also detect chromosome breakage and disruption of the spindle apparatus. At all three exposure periods, no significant increases in micronuclei were found. BaP was used as a positive control in these studies and was given at a dose approximating that expected in the diesel exhaust. In both assays BaP was also negative, suggesting that the sensitivity of these assays was too low for the exposure conditions.

Pereira et al. (1980b) also conducted a micronuclei assay using Chinese hamsters exposed to diesel exhaust for 8 hours per day for 6 months. In this study they found a significant increase in the percentage of polychromatic erythrocytes with micronuclei. The difference found between the mouse and hamster study was not explained. In the same study with hamsters, chromosomal abnormalities in bone marrow cells were also examined. As in the mouse metaphase analysis, no increase in chromosomal abnormalities was observed.

In addition to the other two assays, Pereira et al. (1980b) conducted a sister chromatid exchange (SCE) bioassay with the bone marrow from the exposed hamsters. SCE are produced because of DNA lesions induced by mutagens and may be related to recombinational or postreplicative repair of DNA damage. In this study there was no significant change in the frequency of SCE. There was, however, a decrease in the mitotic index. Guerrero et al. (1980) examined SCE in lung cells of Syrian hamsters treated by either intratracheal instillation of one dose of diesel exhaust particles at 0-20 mg/animal or by inhalation exposure to diesel exhaust with a 6 mg/m^3 particle concentration 8 hours a day for 3 months. Twenty-four hours after the intratracheal instillation or following the 3-month inhalation exposure, the animals were killed, and primary lung cell cultures were established. When the cultures had colonies of 50 cells or more, SCE analysis was performed. A positive dose-response relationship was found for intratracheal doses between 0 and 20 mg/animal. Animals exposed by inhalation to diesel exhaust had no increase in SCE. When the total amount of particles that were expected to be inhaled by the latter group of animals was calculated and compared to the amount administered by intratracheal instillation, it was found to be below the levels that gave positive responses by intracheal instillation.

It has been shown that exposure of mice to known mutagens and carcinogens leads to an increase in the frequency of abnormal sperm. Pereira et al. (1980c) exposed male strain A mice to 18-fold diluted Nissan diesel exhaust with 6 mg/m^3 particle concentration for 31 or 39 weeks; these time periods represent approximately six and eight complete spermatogenic cycles. No detectable changes in sperm morphology were found at either time period. Pereira et al. (1980b) also examined sperm shape abnormality in Chinese hamsters exposed to diesel exhaust for 6 months. In this study there was a significant increase in abnormal sperm. The authors caution that this result was obtained from a small group and should be viewed as preliminary.

Pereira et al. (1980d) also used a rat liver foci assay to examine the genotoxicity of diesel exhaust. This assay is similar to the two-stage mouse skin model for carcinogenesis.

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Rats were given a partial hepatectomy to enhance the rate of cell proliferation and then were exposed to diesel exhaust emissions for 3 or 6 months. During exposure the rats were fed a choline-devoid diet, inducing a dietary deficiency that acts as a promoter. At 3 or 6 months the rats were sacrificed, and their livers were histologically examined for foci of hepatocytes containing gamma glutamyl transpeptidase. Gamma glutamyl transpeptidase is used as a marker for cancerous hepatocytes. No increase in foci was detected after 3 or 6 months of exposure.

4. In Vitro Tests of Extracts of Air Pollution

Extracts of polluted air and of air emissions have been tested for mutagenic and genotoxic activity in a wide range of in vitro systems. These tests are performed more quickly and inexpensively than whole animal studies and can utilize effectively the small amounts of test material usually available in air pollution extracts. In addition, a large number of fractions of the extracts that have been separated on the basis of chemical structure or particle size, can be tested concurrently, allowing for the identification and isolation of the substances responsible for the mutagenic or genotoxic activity. Direct extrapolation of the results of *in vitro* tests to potential human health effects is not yet possible, although several studies have been performed that have established a high degree of correlation between mutagenic and carcinogenic activity for some classes of chemicals.

Of the wide range of in vitro tests, those that have been used in testing air pollutants can be placed in four groups. Gene mutational assays utilize bacterial or mammalian cell cultures to detect single or multiple base changes (mutations) in genes. Larger scale damage to the DNA, in the form of DNA strand breaks and exchanges between chromosomes, is detected in assays using cultured hamster embryo cells, liver cells, hamster ovary cells, and mammalian (human) lymphocytes. The ability of chemicals or extracts to cause aberrations in chromosomes, such as breaks, deletions, and translocations, is tested in both hamster cells and human leukocytes. Transformation assays measure the degree to which substances can alter normal cultured cells to states in which they more closely resemble cancer cells.

Transformation of cells in culture is considered analogous to transformation of cells in vivo. These transformed cells in culture may have morphological and biochemical traits similar to cancer cells. Most important, when a cell that has been transformed in culture is implanted in a syngeneic host, it will form a tumor. A variety of cells has been used in transformation assays, including cells from established cell lines and cells freshly isolated. There are actually two types of cell transformation assays. In one assay, the test compound produces the transformation while in the other assay, the test compound enhances a virally induced transformation of the cell. This latter assay is considered more sensitive than the first one.

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Both these assays give results that correlate well with the results of other tests for carcinogenesis and mutagenesis.

Several studies of these types have been conducted with extracts of air pollution and emission particulate. Freeman et al. (1971) tested benzene extracts of the city air particulates for their capacity to transform rat and hamster embryo cells in culture. Transformation was considered complete if the cells treated with extracts formed tumors when transplanted into neonatal mice. The authors found that the extracts did not transform rat embryo cells but did transform cells that had previously been infected with Rauscher leukemia virus. In these cultures of virus-infected cells, the extracts were 600 times more effective in inducing transformation than an equal amount of pure BaP. In addition to the results seen in rat embryo cells, the extracts transformed both infected and uninfected hamster cells. The infected hamster cells were as sensitive as the virus-infected rat cells; the uninfected cells were one-tenth as sensitive as the virus-infected rat cell cultures.

In another study, Gordon et al. (1973) first removed the PAHs by benzene extraction from particulates collected from Los Angeles air. The residue was further extracted with methanol, and this fraction was tested for transforming ability in cell cultures of Fischer rat embryos or Swiss albino mouse embryos. (The mouse cells, but not the rat cells, had been infected with leukemia virus.) Results were positive in both systems, indicating to the authors that non-PAH carcinogens were present in the extract.

Curren et al. (1981) investigated the transforming activity of dichloromethane extracts of particulates from several types of diesel engines, a gasoline engine, and coke oven and roofing tar emissions. They used the BALB/c 3T3 cells in their assay systems, which included or excluded the metabolic-activating system from rat liver. Several of the extracts showed significant transforming activity, but no clear dose-response relationships were found. The metabolic-activating system reduced the transforming activity of some extracts and did not greatly increase the activity of any extract; this suggested that there were direct-acting agents in the extracts. The most potent extracts came from coke oven emissions and the gasoline engine. These were followed by extracts from a Nissan light diesel engine exhaust and then roofing tar emission. Essentially no activity was found in extracts of exhaust from an Oldsmobile light diesel engine and a heavy diesel engine.

Using the same extract material, Castro et al. (1981) were unable to show any transforming activity in their assay system using Syrian hamster embryo cells. However, when the cells were first infected with simian adenovirus SA7, several extracts were capable of enhancing the viral transformation of the cells. Ranking the extracts according to the lowest effective concentration shows that extract of roofing tar emission >coke oven emission >cigarette smoke condensate >Nissan

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light diesel engine >a gasoline engine and a VW diesel engine. Extract from the Oldsmobile light diesel engine and the heavy diesel engine had little or no activity.

Many other assays have been developed to identify carcinogenic compounds using mammalian cell cultures. Several of these assays have been used to examine the genotoxic or mutagenic activity of diesel engine particulate exhaust extracts and extracts of particulates from other emission sources. Mitchell et al. (1981) used L51784 mouse lymphoma cells to examine the mutagenicity of these extracts. The assay was done with and without a metabolic-activating system. All extracts tested gave positive results in the presence and absence of the metabolic-activating system, indicating the presence of direct-acting mutagens in the extracts. Extract of the gasoline engine exhaust emission was the most potent extract tested. Castro et al. (1981) examined the same extracts for mutagenicity using Chinese hamster ovary cells. In this system, extracts of emissions from the Nissan and Volkswagen diesel engines, the gasoline engine, and coke oven were positive. Unlike the results of Mitchell et al. (1981) with mouse lymphoma cells, extracts of emissions from a heavy diesel engine, the Oldsmobile light diesel engine, roofing tar, and cigarette smoke were not found to be mutagenic. Curren et al. (1981) used mouse BALB/c 3T3 cells in a mutagenicity assay and found extracts of emissions from roofing tar, the Nissan light diesel engine, the gasoline engine, and coke oven to be mutagenic, and the heavy diesel engine and the Oldsmobile light diesel engine not to be mutagenic.

Using Syrian hamster embryo cells, Castro et al. (1981) examined whether the extracts would cause DNA fragmentation. This type of damage induced by chemical agents correlates fairly well with their carcinogenic potential. Only coke oven and gasoline engine emission extracts caused detectable breakage of the cellular DNA.

Mitchell et al. (1981) examined whether these extracts would increase sister chromatid exchanges (SCE) in Chinese hamster ovary cells. Without metabolic activation, all extracts tested showed some activity. Coke oven emission and Nissan light diesel engine exhaust extracts were the most active.

Lockard et al. (1981) examined whether extracts from airborne particulates would increase SCE in human lymphocytes or V79 fibroblasts from Chinese hamster lungs. They used extracts from samples of airborne particulates, collected over a 5-month period on the campus of the University of Kentucky in Lexington. There was a linear dose-related increase of SCE in human lymphocytes with 60-80 μg of extract necessary to induce a doubling in the number of SCE. Several extracts that were positive with human lymphocytes failed to induce an increase of SCE in V79 cells, however, other extracts did cause an increase. BaP was used as a positive control and increased SCE in both cell types. The increase of SCE in human lymphocytes by BaP did not occur in the presence of a metabolic activating system, although, BaP generally needs to be metabolically activated to be effective. The amount of BaP, 8 μg, needed to induce a doubling of the SCE in these cells was much more than was likely to be in the extracts. Therefore, the extracts must have contained active compounds other than BaP.

The most widely used gene mutational assay in testing extracts of air pollution is the Ames assay (Ames et al. 1973, 1974), which measures the rate at which special strains of the bacteria, *Salmonella typhimurium*, mutate or revert to a less specialized form. The assay uses either the test material directly or the test material in combination with a biochemical preparation of liver or lung tissue that metabolizes the test material, thereby testing for the possibility of *in vivo* generation of mutagens. The correlation of positive results in the Ames assay with positive results in long-term carcinogenicity assays has been found to be between 80% and 90% depending on the class of chemical being tested (McCann et al. 1975, Commoner et al. 1976). A recent international study with 42 chemicals found the false positive rate, i.e., the rate at which a positive result was obtained for a noncarcinogen for bacterial assays, to be 5-10% (Bridges et al. 1981).

Gene mutational assays have been used to test air pollution from a number of sites and sources. Using the Ames assay, investigators have detected mutagenic activity in extracts of particulates from residential and urban air (Talcott and Wey 1977, Pitts et al. 1977, Tokina et al. 1977, Commoner et al.

1978, Teranishi et al. 1978, Salamone et al. 1979, Moller and Alfheim 1980, Lockard et al. 1981, Tokiwa et al. 1980, and Walker et al. 1982), in fly-ash from coal-fired power plants (Fisher et al. 1979), in particulates collected from air in tunnels (Ohnishi et al. 1980), and in exhaust from gasoline- and diesel-powered automobiles (Ohnishi et al. 1980, Wang et al. 1981, Huisingh 1981, and Lewtas 1982). One study (Tokiwa et al. 1977) reported higher mutagenic activity in samples taken from an industrial area than in samples from a residential area. In most of the studies, a linear dose-response relationship was observed between the amount of material tested and mutagenic activity (Tokiwa et al. 1976, Tokiwa et al. 1977, Pitts et al. 1977, Teranishi et al. 1978, Commoner et al. 1978, Salamone et al. 1979, Moller and Alfheim 1980, Ohnishi et al. 1980, Walker et al. 1982).

Because the extracts of air pollution are composed of a heterogenous mixture of substances, it is unlikely that the mutagenic activity can be attributed to a single chemical or class of chemicals. Most of the tests, however, have indicated that the airborne mutagens cause the same type of mutation. Tokiwa et al (1977), Teranishi et al. (1978), Salamone et al. (1979), Moller and Alfheim (1980), Ohnishi et al. (1980), Claxton (1980), and Walker et al. (1982) have reported the highest activity of their samples were in the *Salmonella* strains most sensitive to frameshift mutations.

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BaP and other PAHs have been identified in extracts of air pollutants by Talcott and Wei (1977), Tokiwa et al. (1977), Commoner et al. (1978), Dehnen et al. (1978), Salamone et al. (1979), Moller and Alfheim (1980), Ohniski et al. (1980), and Tokiwa et al. (1980). Several studies have indicated that PAHs require metabolic activation by the liver tissue preparation to have a mutagenic effect (Wislocki et al. 1976, Wood et al. 1976). Talcott and Wei (1977) found that 75% of the mutagenicity of their urban air samples was due to an enzyme-activated fraction; this activity was substantially reduced when an inhibitor of the PAH-metabolizing enzymes was added to the culture. Moller and Alfheim (1980), Lockard et al. 1981, and Salamone et al. (1979), however, found extracts from their air pollutant sample usually gave similar results with and without a metabolic-activating system.

Pitts et al. (1980) recently demonstrated that BaP deposited on a glass fiber filter in the presence of ambient levels of ozone is transformed to strong mutagens in the Ames test. This suggests that airborne BaP may not always require metabolic activation to exert a carcinogenic effect, but that is chemically activated in the atmosphere by ozone. On the other hand, the finding indicates that some mutagens found in the particulate extracts may be artifacts of the method of collection and, as indicated below, direct-acting mutagens are found in the extracts.

Analyzing air samples from residential areas, Talcott and Wei (1977), Moller and Alfheim (1980), Salamone et al. (1979), and Tokiwa et al. (1977) observed mutagenic activity that did not require enzyme activation. In later research, Wang et al. (1978) found that the lead content of extracts of non-industrial airborne particulates correlated well with mutagenic activity, suggesting to the authors that the source of the mutagens was vehicular emissions. Further, they detected direct-acting mutagens in extracts of automobile exhaust, although they did not isolate the compound or compounds responsible. Wang et al. (1980) found that extracts from diesel exhaust particulates were mutagenic and that the mutagenicity of the extract was not dependent on metabolic activation by liver homogenate. They actually showed that this activity was reduced by addition of the homogenate. The reduced activity was found not to be from enzymatic activity but from nonspecific binding of the mutagens to the protein in the homogenates instead of the DNA of the bacteria. They showed that glutathione, a natural constituent of the body that can bind to electrophilic compounds, reduced the mutagenicity of the extract, thus suggesting that the mutagens are direct alkylating agents. Claxton (1980) also found that the majority of the mutagenic activity in extracts of diesel exhaust was direct acting. Mutagens in gasoline engine exhaust extracts were partially direct acting, but metabolic activation did increase the mutagenic activity of the extracts. Whether any of the direct-acting mutagenic activity discussed here is artificial because of the method of collection is not known this makes assessments of the extracts more difficult.

In a study designed to determine the size of the particles associated with airborne mutagens, Talcott and Harger (1979) detected the highest activity in particles less than 2 µm in diameter and found that this fraction contained alkylating agents. Fisher et al. (1979) and Tokiwa (1980) also compared particle size and mutagenic activity. Fisher et al. (1979) found that fly-ash particles of 3.2 µm diameter had the greatest mutagenic activity, and Tokiwa et al. (1980) found the highest mutagenic activity and PAH content in particles with diameter of 0.3-1.0 µm. Particles of these sizes readily penetrate lung airways (Kotin 1968).

C. Monitoring Data

A number of substances known to cause cancer in humans or laboratory animals have been detected in ambient air. These substances include PAHs, aza-heterocyclic compounds, vinyl chloride, asbestos, metals, pesticides, N-nitroso compounds, carbon tetrachloride, and many other industrial chemicals.

Table III-1 (in Appendix B) is a compilation of suspected and known carcinogens found in air pollution. This list contains PAHS, pesticides, and inorganic compounds

The presence in air of some of the suspected or known carcinogens listed in Table III-1 has not been established by monitoring, but is highly probable. These compounds are used in industry or are industrial by-products; because of their volatility or association with fume-producing processes, they are likely to enter the air. Alkylating agents such as bis(chloromethyl)ether and chloromethyl methyl ether are potent carcinogens in rodents (Laskin et al. 1971, Leong et al. 1971) and humans (Albert et al. 1975, Lemen et al. 1976, Pasternack et al. 1977, Sakabe 1973). The presence of these substances in ambient air has not been determined, but the stability of bis(chloromethyl)ether in moist air is at least 18 hours (Collier 1972), a period of time long enough for human exposure to occur.

The presence of carcinogenic substances in the ambient air strongly suggests that humans are exposed. However, monitoring data alone are generally inadequate to determine the extent of exposure of individuals. Given that the average person inhales from 10 to 20 m^3/day of air, one can estimate the quantity of the inhaled material to be in the microgram to milligram range.

Particulate air pollution is an important contributing source of known and suspected carcinogens in the air. In addition to the organic compounds, particulate air pollution contains arsenic, beryllium, cadmium, chromium, lead, nickel, and asbestos. As discussed in a review of particulate air pollution by USEPA (1982), there is a multimodal distribution in the size of the particulates. Particles less than 0.1 μm are in the nuclei (Aitken) mode and typically originate from combustion sources. These particles are short-lived because of coagulation of the particles into particulates with the size of 0.1-2.5 μm; the newly formed particles are considered to be in the accumulation mode. Particles making up these two modes are termed fine particles. The final category is of particles greater than 2.5 μm, making up the coarse mode. These particles are usually derived from mechanical processes or wind erosion and are not usually formed to any great extent from fine particles. Fine particles, because of their long residence time and atmospheric formation, can build up far from their source while coarse particles normally occur only near strong source emissions.

As a general historical perspective, total suspended particulate in New York City in the early 1960s contained 10% or less benzene-soluble organic material. Control programs put into effect between the early 1960s and mid 1970s produced a substantial reduction in total suspended particulates. With the reduction of particulates there was a marked decrease in the concentration of benzene-soluble organics and trace elements (USEPA 1982).

A large number of gaseous air pollutants are suspected or known carcinogens. The concentrations of these compounds are usually harder to measure than those associated with particulates because of the difficulty in collecting sufficient amounts to quantify. Singh et al. (1982) has recently reported the results of a 3-year study on gaseous air pollutants. They measured 44 different organic chemicals in 10 cities throughout the United States. In general they found a number of known bacterial mutagens and suspected carcinogens. Most of the compounds measured were in the subparts per billion concentration, although concentrations of aromatic hydrocarbons and formaldehyde averaged 5-20 ppb. The concentrations of anthropogenic compounds were generally one or two orders of magnitude higher in urban air than in rural or clean remote air. Diurnal variations were observed and depended on source strength and prevailing meteorology. Afternoon mixing led to sufficient dilution to produce minimum concentrations of several primary pollutants. Photochemical pollutants showed maximum concentrations in the afternoon.

D. Multimedia Exposure

In addition to exposure to airborne carcinogens by inhalation, studies of the environmental distribution of air pollutants indicate that human exposure can also occur through routes other than inhalation. There is evidence that some substances released into the air, if unaltered chemically, ultimately end up in soil and water or on plants, including edible plants.

Arsenic and lead have been studied for their environmental distribution. Lindau (1977) found arsenic in drinking water (0.08-3.0 µg/liter), soil (5-15 mg/kg), and vegetables and grains (0.1 µg/g). Levels measured in the vicinity of a copper smelter were 500 µg/liter (water), 30 mg/kg (soil), and 0.06 µg/g (barley). Levels were considerably lower in samples taken 40 km from the plant. Studies in 32 areas of the United States showed a correlation between the amount of lead in rainfall

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in a given locality and the amount of gasoline used in that locality (Lazrus et al. 1970). Numerous other studies have demonstrated an inverse relationship between the lead content of grasses and soil and their distance from highways (NAS 1972a). Studies of crop plants indicated that, although the lead content of exposed parts was proportional to air lead concentrations, the levels of lead in the seeds and roots (the edible portions) were unaffected (Motto et al. 1970). After review of this and other studies, the Committee on Lead in the Human Environment of the National Academy of Sciences concluded that most of the lead content of plants, possibly as much as 90-99%, originates from atmospheric pollution. They added, however, that this estimate cannot be applied yet to crop plants, or to the edible portions of crop plants (NAS 1980).

Kotin and Falk (1963) demonstrated that BaP is stable in the atmosphere, both in its crystalline form and when it is adsorbed on soot. Lunde and Bjorseth (1977) showed that BaP can be transported long distances in the air. In the United States, BaP was found in higher concentrations in soil around petroleum and chemical plants (Menck et al. 1974); in the Soviet Union, it was found in higher concentrations in soil around airfields, coke ovens, and oil refineries (Shabad 1980). According to Shabad (1980), levels of BaP in water in the Soviet Union are also higher in industrial areas. Santodonato et al. (1981) summarized multimedia human exposure to polycyclic aromatic hydrocarbons (PAH), Table III-2.

TABLE III-2

ESTIMATED HUMAN EXPOSURE TO PAH FROM VARIOUS AMBIENT SOURCES

(μg/day)

Source	BaP	Carcinogenic PAH[a]	Total PAH
Air	0.0095-0.0435	0.038	0.207
Water	0.0011	0.0042	0.0270
Food	0.16-1.6	b	1.6-16

[a] Total of BaP, BjF, and indeno[1,2,3-cd]pyrene

[b] No data available

SOURCE: Sandodonato et al. 1981

Atmospheric deposition of PAH onto food and into water cannot be considered the only source of PAH exposure via these routes since food preparation and local effluent sources may add to PAH levels.

E. Summary

This chapter compiles and summarizes experimental evidence and monitoring data. A substantial number of studies has shown that extracts of airborne materials from polluted air and materials emitted from motor vehicle engines and stationary sources are frequently carcinogenic and mutagenic when tested in experimental bioassay systems. Results of in vivo tests have included the induction of skin cancers, lymphomas, fibrosarcomas, liver tumors and lung tumors in mice, lung tumors in rats and hamsters, and chromosome damage and sister chromatid exchange in hamsters. Respiratory irritants present in polluted air may also enhance the effects of other carcinogenic agents. Results of in vitro tests have included the induction of point mutations in bacteria and *Drosophila melanogaster*, malignant transformation of mammalian cells in culture, and sister chromatid exchange and DNA fractionation in cultured mammalian cells, including human cells. Positive results in these *in vitro* tests are generally correlated with the potential for carcinogenicity.

Table III-1 (in Appendix B) lists more than 50 chemicals that have been detected in ambient air and that are known or suspected to be carcinogenic in humans or in experimental animals. Where comparative data are available, concentrations of these chemicals tend to be higher in urban areas than in rural areas, and higher still in industrial emissions. There is evidence of significant multimedia exposure to several pollutants after their release into ambient air.

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IV. QUANTITATIVE ESTIMATES

A. Introduction

Chapters II and III have reviewed the qualitative evidence for an association between air pollution and cancer rates. This chapter reviews and summarizes estimates of the possible magnitude of this association--i.e., the number of cancers that might be "attributable" to exposure to air pollution. It should be emphasized that quantitative estimates of this kind can be made (with caution, of course) even if the qualitative evidence for the association is not regarded as fully conclusive. The "softer" the evidence that is used the wider is the possible range of resulting estimates. The question addressed in this chapter is the following: If air pollution is a causative factor in human cancer, what estimates can be made of the fraction of human cancers to which it contributes?

It should be emphasized that the word "contributes" in this question does not imply that air pollution would operate independently as a single causative factor. As emphasized earlier, most cancers have multiple causes, and there is evidence that air pollution may act in conjunction with other factors to increase the risk of cancer. Some reviewers have recognized this by assigning a certain fraction of cancers to more than one causative factor. One way that has been used to develop estimates of the fraction of cancers "attributable" to air pollution is to "subtract out" the effects of other factors.

This is almost certain to lead to underestimation of the contribution of air pollution, by subtracting out the cancers attributable to the joint action of these other factors with air pollution and attributing them solely to the other factors.

B. General Estimates

Because of the limitations inherent in the epidemiologic studies, estimates of what percentage of human cancers may be attributable to air pollution have been the subject of disagreement. Several participants in the recent EPA rulemaking cited estimates by Higginson and Muir (1979, 1976) and Wynder and Gori (1977) that no more than one percent of total cancer deaths are attributable to air pollution. The data on which these estimates are based were not fully described, but these estimates appear to be "subtracted out" estimates, since in both reviews the fractions of human cancer rates attributed to various factors add up to 100%. Hence, these authors implicitly excluded multiple causation.

The most extensive recent review of data providing evidence for associations between cancer and environmental factors is that of Doll and Peto (1981). In the conclusion of their review (Table 20), they proposed 2% as the "best estimate" of the percentage of all cancer deaths attributable to pollution of all kinds, with a "range of acceptable estimates" extending from less than 1% to 5%. Although the basis for these figures is not completely clear, they appear to have been based on the estimates of Pike et al. (1975) and Cederlof et al. (1978), both of which were cited for the conclusion that urban air pollution (as characterized by BaP) might have contributed to about 10% of lung cancer in big cities, i.e., about 1% of all cancers in the country as a whole. The effects of industrial emissions were regarded as negligible, and cigarette smoking was considered sufficient to account for most, if not all, of the patterns of variation in lung cancer rates, including urban/rural differences. A critique of this secondary review paper is presented in Appendix E.

Shy and Struba (1982) presented another review of the scientific evidence on air pollution and cancer. While citing some of the epidemiologic and experimental evidence reviewed in this report, they concluded that "firm conclusions about air pollution and lung cancer are simply not warranted by the current state of knowledge." Although they did not make quantitative estimates of the possible magnitude of the association, they discussed attempts to estimate the risks from exposure to BaP by linear extrapolation from data on occupationally exposed workers, and concluded that such extrapolation "would support an extremely low risk (0.1 to 0.01 of a two to threefold excess) for ambient air." A risk of this magnitude would constitute between 1% and almost 20% (between 0.01(2-1) and 0.1(3-1)) of all lung cancers, and thus would fall within the range of other estimates discussed in this chapter. Further comments on Shy and Struba's review are presented in Appendix E.

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C. Estimates Based on Analysis of Epidemiological Data

A number of investigators have attempted to derive estimates of the quantitative relationship between lung cancer rates and air pollution, using BaP and other substances as indices. Although we believe that BaP has become less and less useful as an indicator of generalized air pollution over time, we report 12 published estimates:

- NAS (1972b) based on the data of Carnow and Meier (1973)
- Pike et al. (1975) based on the data of Doll et al. (1965, 1972)
- Pike et al. (1975) based on the data of Stocks (1957)
- Wilson et al. (1980) reviewing estimates of Pike et al. 1975
- Pike and Henderson (1981)
- Lave and Seskin (1977)
- Doll (1978)
- Cederlof et al. (1978)
- Wilson et al. (1980) based on the data of Hammond et al. (1976)
- Wilson et al. (1980) based on a review of several of the above estimates
- CAG (1978)
- CAG (1982)

We also present an independent estimate, based on analysis of data of Hammond and Garfinkel (1980), as reassembled by Goldsmith (1980), and not based on BaP levels. (The data cited by Hammond and Garfinkel on ambient levels of pollutants were based on observations made after the mortality from lung cancer had occurred. These after-the-fact data are not used in our independent computation.)

An earlier review by the National Academy of Sciences' Committee on Biologic Effects of Atmospheric Pollutants (NAS 1972b) laid out the argument for using BaP as an air pollution indicator:

> It appears, then, that there is an "urban factor" in the pathogenesis of lung cancer in man. The polycyclic organic molecule mentioned most prominently in this report has been benzo[a]pyrene. It was felt that benzo[a]pyrene could be used as an indicator molecule of urban pollution, implying the presence of a number of other polycyclic organic materials of similar structure that may also have some carcinogenic activity. The standard measure of benzo[a]pyrene concentration in the air is the number of micrograms per 1,000 m^3 of air. On the basis of epidemiologic data set against information regarding the benzo[a]pyrene content of the urban atmosphere, one can develop a working hypothesis that there is a causal relation between air pollution and the lung cancer death rate in which there is a 5% increase in death rate for each increment of urban air pollution. In this study, an increment of pollution corresponded to 1 µg of benzo[a]pyrene per 1,000 m^3 of air. On the basis of this assumed relation, a reduction in urban air pollution equivalent to 4 benzo[a]pyrene units (i.e., from 6 µg/1,000 m^3 to 2 µg/1,000 m^3) might be expected to reduce the lung cancer death rate by 20%. These data, however, are not to be interpreted as indicating that benzo[a]pyrene is the causative agent for lung tumors. There is much to support the idea of synergism or cocarcinogenesis, especially with respect to cigarette smoking. In addition, the carcinogenic significance of other polycyclic organic molecules in urban air pollution should be determined.
>
> (NAS 1972b, p. 246)

However, BaP seems to have become less useful, with time, as a general indicator of air pollution. A recent review of problems associated with air pollution (Karolinska Institute Symposium on Biological Tests in the Evaluation of Mutagenicity

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and Carcinogenicity of Air Pollutants, 1982), scheduled for publication in Environmental Health Perspectives (major authors, Lars Freiberg and Norton Nelson) came to the conclusion:

> At the present time there is no way to quantitate how changes in air pollution levels may have reduced mortality from lung cancer because there has been a lack of a completely reliable indicator of air pollution carcinogenicity.

The Karolinska 1982 review repeated the conclusions of an earlier review (Cederlof 1978)

> combustion products of fossil fuels in ambient air, probably acting together with cigarette smoke, have been responsible for cases of lung cancer in large urban areas, the numbers produced being of the order of five-ten cases per 100,000 per year

and indicated no basis for any revision in the conclusions drawn by NAS (1972b) in view of current data. Five to 10 cases per 100,000 per year is about 6 to 15% of all lung cancer cases.

There is evidence that BaP levels have decreased in the United States (CEQ 1980) in the past 20 years, without a proportional decrease in all other air pollutants--thus currently making BaP a poor index of trends in air pollution levels. In 1958-59, the median level of BaP measured in urban air was about 6 ng/m^3 (range, 1-60 ng/m^3), and that in rural air was about 0.4 ng/m^3 (Sawicki et al. 1960). By the mid-1960s the median level at urban sites was reduced to 3.2 ng/m^3, and by the mid-1970s it was reduced to below 1.0 ng/m^3 (Wilson et al. 1980, CEQ 1980, Shy and Struba 1982). Although earlier measurements are not available for the United States, Shy and Struba (1982) suggested that levels in the 1930s and 1940s would have been several-fold higher. Wilson et al. (1980) cited data compiled by Ludwig et al. (1971), which showed that dustfall rates declined by a factor of about 2 in Pittsburgh, Cincinnati, and Chicago between 1935 and 1958, and by the same factor in New York City between 1945 and 1958. Since much of the dustfall in these urban areas was associated with incomplete combustion of fossil fuels in these periods, dustfall rates may provide a surrogate measure of likely changes in BaP levels. However, there was no marked change in dustfall rates between 1958 and 1966, a period in which the data cited above suggest a substantial decrease in BaP levels. Levels of BaP in the United Kingdom in the mid-1970s were several times higher than in the United States, probably in the range of 3-5 ng/m^3 (Lawther 1980, Wilson et al. 1980).

One consequence of the changes in BaP levels since the 1950s (or earlier) is that differences between regions (e.g., between urban and rural areas) have been reduced (CEQ 1980), so that associations between air pollution (as measured by BaP) and cancer rates are more difficult to demonstrate. Comparison of cancer rates with contemporaneous BaP levels is likely to overestimate the strength of the relationship between them, because cancer rates are actually influenced by exposures 20 or more years earlier, when BaP levels (and differentials) were higher. Also, as discussed in Section II.B.5.d., levels of other carcinogenic components of ambient air have probably increased, while those of polynuclear aromatic hydrocarbons

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(of which BaP serves as an index) have decreased. Hence, applying the relationship of cancer rates to BaP levels at some time in the past will overstate the BaP effect per unit dose and will underestimate the hazards posed by present-day ambient air, and hence will underestimate the contribution of present-day exposures to future cancer risks.

Recognizing these difficulties, we have summarized in Table IV-1 the estimates made by others of the dependence of lung cancer rates on BaP levels. Most of these estimates were obtained by linear regression techniques (i.e., calculation of the linear relationship between differentials in lung cancer rates and differentials in BaP levels). Hence, the dependence of lung cancer rates on air pollution levels is expressed in units of incremental lung cancer rate per ng/m^3 of BaP.

The 13 estimates reviewed above are listed in the second column of Table IV-1. In comparing these estimates, it should be recognized that they fall into two categories that are not strictly comparable. The estimates by CAG (1978, 1982), Pike et al. (1975) based on data of Doll et al. (1965, 1972), Pike and Henderson (1981), and Wilson et al. (1980) based on data of Hammond et al. (1976), were based on studies of workers occupationally exposed to products of incomplete combustion. In these studies BaP was used as an index of exposure to these products. The remaining estimates were based primarily (or entirely) on studies of the general population exposed to ambient air, and used BaP as an index of exposure to a wider mixture

TABLE IV-1

ESTIMATES OF LUNG CANCER DEATHS ASSOCIATED WITH VARIOUS BaP LEVELS

Source	Estimated Dose-Response Coefficient (Lung cancer deaths[1]/year per ng/m^3 BaP)	Adjusted[2] Dose-Response Coefficient (Lung cancer deaths[1]/year per ng/m^3 BaP)	Deaths/Year Per 100,000	
			At Mean Level of 6.4[3] ng/m^3 BaP	As % of U.S. Total 1975[4]
NAS 1972b, Carnow and Meier 1973	2x10^{-5}	1.0x10^{-5}	6.4	16
Wilson et al. 1980	1x10^{-5}	0.5x10^{-5}	3.2	8
Pike et al. 1975 (data of Doll et al. 1965, 1972)	*0.4x10^{-5}	*0.4x10^{-5}	2.6	6.5
Pike et al. 1975[1] (data of Stocks 1957)	1.4x10^{-5} (smokers) 0.4x10^{-5} (nonsmokers)	1.4x10^{-5} (smokers) 0.4x10^{-5} (nonsmokers)	5.2	13
Wilson et al. 1980 (review of Pike et al. 1975)	*0.8x10^{-5}	*0.8x10^{-5}	5.2	13
Pike and Henderson 1981	*0.8x10^{-5}	*0.8x10–^{5}	5.2	13
Lave and Seskin 1977	1.3-5.0x10^{-5}	0.3-1.2x10^{-5}	2-8	5-20
Doll 1978	2.9x10^{-5} (smokers) 1.5x10^{-5} (nonsmokers)	0.7x10^{-5} (smokers) 0.35x10^{-5} (nonsmokers)	4.5 2.2	11 5.5
Cederlof 1978	1.2-2.4x10^{-5}	0.3-0.6x10^{-5}	2.1-4.2	5-10
CAG 1978	*0.11x10^{-5}	*0.11x10^{-5}	0.7	2
Wilson et al. 1980 (data of Hammond et al. 1976)	*0.2x10^{-5}	*0.2x10^{-5}	1.3	3
CAG 1982	*0.14x10^{-5}	*0.14x10^{-5}	0.9	2.2
This report (data of Hammond and Garfinkel 1980)	2.2x10^{-5}	1.1x10^{-5}	7.0	17

[1] Standardized to 1970 U.S. population

[2] Adjusted by assuming that effective population exposure was twice that recorded in the period 1958-69 (see text)

[3] Average urban levels, early 1960s, multiplied by 2 to allow for likely reduction since 1935-45 (see text)

[4] The lung cancer mortality rate in the United States in 1975 (age adjusted to the 1970 population) was approximately 67 deaths/per 100,000 among males and 40 deaths per 100,000 among the entire population (see Appendix C). Since some studies made estimates for males only, we have developed a factor to convert the risk in males to the risk in the general population, by assuming that the risk among nonsmokers is the same for males and females, and that the risk among women smokers is approximately half the risk in men smokers. Given these assumptions, we find that the risk of lung cancer deaths among the general population is 82% of that in males (see Appendix D).

*Based on studies of workers exposed to products of incomplete combustion (see text)

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of materials. The fact that the worker studies yield lower estimates of dose-response coefficients ($0.1-0.8 \times 10^{-5}$) than the population studies ($0.8-5.0 \times 10^{-5}$) ($p<0.01$, Mann-Whitney test) suggests that products of incomplete combustion may be associated with only a part of the excess of lung cancers in urban areas, thus making BaP a poor indicator of total air pollution.

The principal limitation in quantifying the population studies is that they all relate cancer deaths observed in the period 1959-1975 to BaP levels measured or estimated for the period 1958-1969. If levels of BaP and related products of incomplete combustion were higher in the 1930s and 1940s (more coal-burning emissions, but fewer automobiles), these studies would overestimate the dose-response coefficient between lung cancer rates and BaP levels. As an illustration of the likely magnitude of this effect, we present in the third column of Table IV-1 adjusted estimates of the dose-response coefficient, derived by assuming that the effective population exposure to polluted air for cancers developing in the 1960s and later was in the period 1935-45, and that levels of BaP at that period (using dustfall rates as a surrogate index of likely BaP levels, as discussed above) were about twice those measured in the early 1960s. For the estimates based on European studies (Lave and Seskin 1977, Doll 1978, Cederlof et al. 1978), the figures in the second column were based on a value of 3.5 ng/m^3 for the urban-rural differential in BaP levels, which was appropriate

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for the mid-1970s. We have adjusted these European figures by a factor of 4 to account for the assumed reduction in BaP levels since the period 1935-45. Estimates based on studies and occupationally exposed workers have not been adjusted.

To place these estimates of dose-response relationships in quantitative perspective, the last two columns in Table IV-1 present calculations of the number of lung cancer deaths that could be attributed to air pollution characterized by 6.4 ng/m^3 of BaP. This is approximately twice the average level of BaP to which the U.S. population was exposed in the mid-1960s, and hence is the average level of BaP to which we have assumed the U.S. population was exposed in the period 1935-45. The figures in the last two columns of Table IV-1 are derived by multiplying the "adjusted" dose-response coefficients in the third column by 6.4 ng/m^3. These figures give estimates of the number of lung cancer deaths in the 1960s (per 100,000, expressed as a percentage of total U.S. lung cancer deaths in 1975; this percentage is an understatement of the percentage of deaths in the 1960s related to BaP exposure) attributable to air pollution levels in prior decades. The estimates based on studies of the general population fall into the range between 2 and 8 deaths/year per 100,000 people, or between 5% and 20% of the lung cancer rates in the mid-1970s. The estimated median from these population studies is 4.5 deaths/year per 100,000, or about 11% of the almost 90,000 lung cancer deaths in the United States in 1975.

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These estimates of the contribution of BaP-indexed air pollution to lung cancer rates in the 1960s are not sensitive to changes in our assumption about BaP levels in the period 1935-45. If we had assumed a higher figure for average BaP levels in that period, our estimates of adjusted dose-response coefficients in the third column of Table IV-1 would have been lower, but the multiplier used to derive the estimates in the last two columns would have been correspondingly higher.

Despite the relative stability of these estimates, they unfortunately cannot be used to generate reliable estimates of the future effects of present air pollution, or even to make firm estimates of the contribution of past air pollution to current cancer rates. This is because BaP is not a stable index of the carcinogenicity of polluted air. Although the general population exposure to BaP and to other products of incomplete combustion has decreased considerably since the 1950s, it appears unlikely that the carcinogenicity of polluted air has decreased in direct proportion. The fact that BaP levels relative to other air pollutants have changed with time implies that all the estimates in Table IV-1 are time-dependent, and unfortunately cannot be used to predict the future consequences of present-day air pollution using BaP levels as a surrogate for all air pollution.

Despite these limitations, each of the studies listed in Table IV-1 is considered in more detail below.

Carnow and Meier (1973) estimated the risk of lung cancer mortality by relating 1960 deaths to 1968 levels of BaP. Wilson et al. (1980) reduced this estimate (NAS 1972b) by half to 1.0 death/10^5 persons per ng/m^3 of BaP. Wilson cited monitoring data from 28 sites in 1959, which seemed to indicate that levels of BaP had declined. There are few data on levels of BaP before 1966, and it is not possible to establish whether or not Wilson et al.'s correction was appropriate. The more complete monitoring data available from 1966 to 1977 indicate that levels from 1966 to 1969 were steady or slightly increasing (CEQ 1980) and then declined. Thus, we do not know whether or not Wilson et al.'s correction of Carnow and Meier's estimate is the same as the adjustment we have applied in Table IV-1 to allow for likely reduction in BaP levels prior to 1959. For this reason, either of the two adjusted estimates may be appropriate.

Pike et al. (1975), assuming a linear relationship between exposure and carcinogenic response, extrapolated the results of a study of gas workers by Doll et al. (1965, 1972) to the general population:

> The carbonization workers were exposed to an estimated 2,000 ng/m^3 BP for about 22 percent of the year (assuming a 40-hour working week, 2 weeks paid leave, 1 week sick leave); very roughly, the men were exposed to the equivalent of 440 (2000 x 0.22) ng/m^3 BP general air pollution. This exposure caused an extra 160/10^5 lung cancer cases, so that we may estimate, assuming a proportional effect, that each ng/m^3 BP causes 0.4/10^5 (160/10^5 divided by 440) extra lung cancer cases per year. A city with 50 ng/m^3 BP air pollution might, therefore, have an extra 18/10^5 lung cancer cases per year. These numbers are not negligible, although they are small when compared, say, to smoking a pack of cigarettes every day.
> (Pike et al. 1975, p. 231)

Thus, based on the experience of carbonization workers, Pike et al. (1975) estimated the risk of lung cancer mortality as 0.4 deaths/10^5 persons per ng/m^3 of BaP.

Wilson et al. (1980) reexamined this estimate by Pike et al. (1975) and included a doubling factor to correct for the fact that the gas workers were not exposed for all of their lives, leading to an estimate of 0.8 deaths/10^5 persons per ng/m^3 BaP. However, neither Pike et al. (1975) nor Wilson et al. (1980) made any further adjustment for the fact that the gas workers were not all followed up to their deaths. Because the incidence of human lung cancers increases in proportion to the 4th or 5th power of age (or duration of exposure) the possibility exists that Pike et al. (1975) and Wilson et al. (1980) have underestimated the full lifetime cancer risks, probably by a factor of 3 or more. For example, comparing exposures beginning at birth, and continuing for a lifetime with industrial exposures beginning at age 20 and assuming a 73-year life span, implies a ratio of $(73/53)^4=3.6$). Thus Pike et al.'s original estimate may be as low as one-sixth or one-seventh of the appropriate estimates. However, we have not amended either estimate to take account of this factor.

Pike et al. (1975) also used the data of Stocks (1957) to obtain a second estimate.

> Second, there should be an increased lung cancer rate in high PAH-polluted areas [25]; the effect is magnified in most studies when we consider the joint effect of urbanization and cigarette smoking. Table 2 presents data [26] comparing rates in Liverpool to those in rural North Wales. This study

> by Stocks was done in an area of "stable" air pollution. A fair summary of these data is that the urban effect produces an excess of $28/10^5$ lung cancer deaths in nonsmokers and $100/10^5$ such deaths in smokers, the latter figure being independent of the actual amount smoked. We might refer to this increase as a modified additive effect. The difference in BP levels in the air between the two areas was estimated to be 70 ng/m^3 (77 ng/m^3 compared to 7 ng/m^3); thus, we may very crudely estimate the air pollution effect in the presence of cigarette smoking at $1.4/10^5$ per ng/m^3 BP or $0.4/10^5$ per ng/m^3 BP in nonsmokers (Table 3).
>
> (at pp. 231-232)

Based on the prevalence of smoking in the United States in the recent past (i.e., approximately one-third of all adults are smokers), this estimate leads to a risk of lung cancer mortality of 0.8 deaths/10^5 persons per ng/m^3 of BaP. (If based on earlier smoking habits, this estimate would be higher; Wilson et al. (1980) listed this estimate as 1 death/10^5 persons, possibly because it was based on past smoking habits.) This estimate may be low, if, as appears likely, the estimated average difference in BaP levels between urban and rural areas is great.

Pike and Henderson (1981) estimated the quantitative relationship between lung cancer risks and exposure to cigarette smoke (data from various sources), coke oven emissions (data from Lloyd 1971 and Redmond et al. 1972), and hot pitch fumes (data from Hammond et al. 1976). They calculated that exposure to about 15 ng/m^3 BaP could be equated to smoking 1 cigarette/day, and hence estimated the "single cause lifetime risk" of lung cancer to age 70 resulting from ambient air exposure to 1 ng/m^3 BaP as 73×10^{-5}. This corresponds to an age-standardized lung cancer rate of about 0.8×10^{-5} deaths/year per ng/m^3 BaP.

Carnow (1978) suggested a number of factors that may have led Pike et al. (1975) to an underestimation of risk. Although Pike et al.'s estimates of the risk of lung cancer mortality may be low, it is likely that the ratio of 3.5 in risk between smokers and nonsmokers (1.4/0.4 = 3.5) is reliable, although, 3.5 is lower than the usual estimates of the relative risks of smokers. The difference (3.5) was reported by Wilson et al. (1980) to be statistically significant. This difference, plus some reasonable assumptions, permits estimation of the average risk to the general population from data on males alone (see Appendix D). The general population excess is about 82% of the male excess.

Based on extensive regression analyses of lung cancer mortality and air pollution levels, Lave and Seskin (1977) suggested that

> ... if the quality of air of all boroughs (England) were improved to that of the borough with the best air, the rate of death from lung cancer would fall by between 11 and 44 percent.

This corresponds to 4.4-17.6 deaths/10^5 persons at British levels of pollution (assumed to be 3.5 ng/m^3 of BaP) or 1.3-5.0 deaths/10^5 persons per ng/m^3 of BaP.

Doll (1978) estimated that the risk of lung cancer mortality attributable to urban air pollution in Europe was no more than 10 deaths per 10^5 smokers and no more than 5 deaths per 10^5 nonsmokers. Based on current U.S. smoking habits, this estimate corresponds to 6.7 deaths/10^5 persons or 1.9 deaths/10^5 persons per ng/m^3 taking average levels of BaP to be 3.5 ng/m^3 in Europe.

Doll (1978), however, provided data to indicate that levels of BaP ranged much higher than 3.5 ng/m^3 in highly urban areas of Britain. Doll (1978) also estimated the attributable risk in smokers to be twice the risk in nonsmokers, which is lower than the 3.5-fold ratio derived by Pike et al. (1975). However, it is not possible to ascertain whether the former is too high or the latter is too low since the ratio cited by Doll (1978) was a personal estimate of the author and not based on any specific calculation or data. No data were cited to support Doll's estimates of attributable risk.

Cederlof et al. (1978), summarizing the conclusions of a conference on air pollution and long-term health effects, stated:

> Combustion products of fossil fuels in ambient air, probably acting together with cigarette smoke, have been responsible for cases of lung cancer in large urban areas, the numbers produced being of the order of 5-10 cases per 100,000 males per year [European standard population]. The actual rate will vary from place to place and from time to time, depending on local conditions over the previous few decades. (at p.9)

This estimate was a synthesis of material presented at a conference, and the basis for it was not provided in detail. Taking the risk to the general population as 82% of the risk to males (see Appendix D) and average European levels of BaP as 3.5 ng/m^3, this estimate corresponds to 1.2-2.4 deaths/10^5 persons per ng/m^3 BaP.

The Carcinogen Assessment Group (CAG 1978) of the Environmental Protection Agency reviewed a number of epidemiological and animal studies in an attempt to estimate the "excess lung cancer incidence" resulting from lifetime exposure to polycyclic organic compounds. For their overall estimate, CAG (1978) took the geometric mean of the estimates derived from four epidemiologic studies. (Using the geometric mean produces lower estimates than using the arithmetic mean. If risk is linearly related to exposure, the arithmetic mean is more appropriate.) This overall estimate was expressed as 0.28% excess lung cancer "incidence" (a slight misnomer since all the studies were mortality studies) per ng/m^3 of BaP. As a percentage, this estimate is a ratio of the estimated excess lung cancer mortality rate to the background rate. This would correspond to about 0.11 deaths/10^5 persons per ng/m^3 BaP.

By expressing the estimate in this way, CAG (1978) assumed that the effect of exposure to each ng/m^3 of BaP is dependent on the background rate of lung cancer mortality in the exposed population. This means that if the background rate is high, the effect would be large, but if the background rate were low, there would be little or no effect. It is reasonable to expect that the magnitude of the effect attributable to BaP will vary as a function of the presence or absence of substances (such as cigarette smoke or other carcinogenic air pollutants) that interact with BaP in the induction of cancer. However, it is not clear why this variation should otherwise depend on the background mortality rate of lung cancer.

In 1982, CAG (1982) updated one of the 1978 estimates. Reviewing the results of epidemiological studies of workers exposed to coke oven emissions, they estimated that the unit risk (for males) of dying from lung cancer as a result of a working lifetime of exposure to BaP is 9.25×10^{-5} per ng/m^3 of BaP. This corresponds to a rate of about 0.14×10^{-5} deaths/year per ng/mg^3 of BaP. However, this estimate is not comparable with some others in Table IV-1, because it was calculated exclusively for exposure to products of incomplete combustion (as indexed by BaP), whereas others were calculated for air pollution (as indexed by BaP) with other pollutants assumed to be present in proportion to the BaP values. The latter type of calculation includes the effect of compounds of air pollution other than products of incomplete combustion (such as asbestos and synthetic organic chemicals), whereas CAG's 1982 estimate does not. CAG's 1978 estimate appears to have included and averaged estimates of both types.

Wilson et al. (1980) derived an estimate of lung cancer mortality of 0.2×10^5 per ng/m^3 BaP using the data of Hammond et al. (1976) on a group of roofers and waterproofers working with pitch and asphalt. The estimate appears to be too low, primarily because the comparison group was made up of other members of the workers' own trade union, and this would tend to underestimate the risk if other members of the trade union were already at increased risk of lung cancer, as seems likely from other occupational studies.

The estimates made by Carnow and Meier (1973), Pike et al. (1975), Hammond et al. (1976), CAG (1978), and some animal studies of benzo[a]pyrene, assembled by Wilson et al. (1980)

indicated that the effect of BaP in the animal studies is much less than the "enhanced" effect attributable to BaP from occupational or urban epidemiological studies. The arithmetic mean of the estimates from the epidemiological studies led Wilson et al. (1980) to what they called a "best estimate," of 0.5 deaths/10^5 persons per ng/m^3 of BaP. There are several problems with this "best" estimate, not least of which was that several of the separate estimates (Carnow and Meier 1973, Pike et al. 1975, and Hammond et al. 1976) appear to have entered Wilson's calculations more than once.

The estimates derived by CAG (1978) differ from those made by Wilson et al. (1980) (in their Table 5-4) from the same studies. For example, Wilson et al. (1980) estimated the Carnow and Meier (1973) response coefficient as 1.0 death/10^5 persons per ng/m^3 of benzo[a]pyrene. CAG (1978) reduced this estimate to less than one-tenth of the figure estimated by Wilson et al. (1980). Also, as indicated earlier, the estimate of Pike et al. (1975) based on the data of Doll et al. (1965, 1972) was modified by Wilson et al. (1980) to 0.8 deaths/10^5 persons per ng/m^3 of BaP. In the CAG (1978) analysis, this figure was given as 0.57 deaths/10^5 persons per ng/m^3 of BaP (160/10^5 divided by 283 ng/m^3 of BaP) and then converted to a percentage by dividing by an anomalously high background rate of lung cancer mortality (0.57/10^5 divided by 200/10^5=0.285%). This final CAG estimate is close to CAG's overall figure of 0.28% and converted to 0.12 deaths/10^5 persons by Wilson et al. (1980)

(0.28% x 40 deaths/10^5 persons = 0.11/10^5). (Note that Wilson et al. used a background rate of 40/10^5 persons, while CAG used a background rate of 200/10^5 persons--a five-fold difference. The age-adjusted mortality rate in the United States for all respiratory cancers--i.e., lung cancer plus others--was 45.9/10^5 persons in 1979.)

The last estimate listed in Table IV-1 was developed for this report and takes account of criticisms and suggestions made concerning earlier estimates (Clement 1981, Karch and Schneiderman 1981). The detailed derivation of this estimate is given in Appendix E. The estimate follows from the lung cancer mortality data of Hammond and Garfinkel (1980) as reassembled by Goldsmith (1980), standardized for age and smoking, stratified by occupational exposure and location of residence. These data show significant effects of urban residence and occupational exposure independently,[1] and we calculate an attributable risk of 13% for occupationally exposed and 12% for non-exposed categories. It is likely that these figures are biased downwards (possibly by factors between 1.4 and 3.3, as discussed on p. E-8) because of selection bias in the study population. The population studied by Hammond and Garfinkel was more suburban, higher percentage white, lower percentage blue collar, more educated than the U.S. population as a whole. However, no attempt is made to correct for this bias here.

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[1] Both Hammond and Garfinkel (1980) and Goldsmith (1980) expressed the opinion that these data did not show a convincing effect attributable to air pollution. However, neither set of authors analyzed the data in the way presented here (in Appendix E) to test the effect of urban residence. Hammond and Garfinkel (1980) reported no statistical association between lung cancer rates in the 1960s and measures of air pollution that were made in 1968. They apparently assumed that no change in pollution (relative or absolute) had taken place between the 1940s--when the cancer cases that appeared in the 1960s were initiated--and 1968 when their two air pollution measures were made.

D. Summary

This chapter summarizes attempts to estimate the possible magnitude of the association between lung cancer mortality rates and air pollution levels. The index of air pollution most commonly used has been the average atmospheric concentration of benzo(a)pyrene (BaP). Using this index, however, creates problems because average levels of BaP in the United States have declined considerably since 1966 and probably were still higher prior to 1966. However, it is not clear that overall hazards posed by air pollution should have declined proportionately, because there is evidence that levels of other potential carcinogens have increased since 1940. BaP is thus no longer a stable index of the carcinogenicity of polluted air, and estimates made for one time period cannot be applied directly to others. Thus, the estimates based on study of lung cancers in the past cannot be used directly to predict future effects of current pollution.

Recognizing this problem, Table IV-1 tabulates 13 estimates (but not based on 13 independent studies) of the quantitative relationship between lung cancer rates and air pollution levels as indexed by BaP concentrations. Estimated slopes (regression coefficients) of this relationship range from 0.1-5.0 x 10^{-5} lung cancer deaths/year per ng/m^3 BaP. Some of these figures should probably be adjusted downwards by factors of 2 to 4 to take account of the likely reduction in BaP levels since the 1930s and 1940s when most effective exposures took place. The estimates derived from studies in the general population (0.8-5.0 x 10^{-5}) are significantly higher than those derived from studies of workers exposed to products of incomplete combustion (0.11-0.8 x 10^{-5}). This difference suggests that incomplete combustion products are associated with only part of the excess lung cancer rates observed in urban areas. Most of the studies were based on lung cancer mortality data from the 1960s, and the results are consistent with the hypothesis that at that time factors responsible for the urban excess in lung cancer were associated with about 11% of lung cancers in the United States. In the one study in which both cigarette smoking and potential industrial exposure could be accounted for, this estimate was about 17%. These quantitative estimates can be derived without resolution of the issue whether the unexplained urban excess of lung cancer can or cannot be attributed confidently to air pollution, which depends on interpretation of data summarized in Chapter II.

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APPENDIX A

TABLE II-1.

Urban-Rural and Other Geographic Studies of Cancer: Code to Comments

a.	Limited information on types, duration, and intensity of exposure
b.	Smoking habits not taken into account in design or analysis
c.	Occupational exposures not taken into account in design or analysis
d.	No information on socioeconomic variables
e.	Dilution effect occurs due to migration
f.	Dilution effect occurs due to labelling all residents of certain geographic areas as "exposed" or "not exposed"
g.	Cause of death as recorded on death certificate may be inaccurate
h.	SMR may be biased when numerators (counts of death) are based on death certificates and denominators (population counts) on census data

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APPENDIX A

TABLE II-1. URBAN-RURAL AND OTHER GEOGRAPHIC STUDIES OF CANCER: A. ECOLOGIC STUDIES

Author/Date	Population	Sites Investigated	Risk Indicator	Other Variables	Principal Findings	Comments*
Blot and Fraumeni 1975	White; male/female; 71 smelting and refining counties	Lung cancer mortality, 1950-1969	No. workers/county in primary smelting and refining of nonferrous ores	Same as Blot and Fraumeni 1976, plus median family income	Lung cancer mortality significantly higher among males and females in group of smelting and refining counties with copper, lead, and zinc industries than in rest of U.S.	a,b,c, d,e,f, g,h
Blot and Fraumeni 1976	White/Nonwhite; male/female; 3056 U.S. counties	Lung cancer mortality, 1950-1969	No. of workers/county in each of 18 manufacturing categories	Population density; percent urban; percent rural farm; percent foreign parentage; median no. school years	Lung cancer rates for white males and nonwhite males increased with urbanization. Excessive rates of lung cancer among males in counties with paper, chemical, petroleum, and transportation industries	a,b,c,
Blot et al. 1977	White; male/female; 39 petroleum industry counties	Cancer mortality for 23 sites, 1950-1969	No. workers/county in the petroleum industry	Population density; percent urban; median no. school years completed by adults; median family income; percent nonwhite; percent foreign parentage	Male residents of petroleum industry counties experienced significantly higher rates for cancer of lung, nasal cavities and sinuses, and skin compared to male residents of control counties. Among white females lung cancer rates were elevated in PIC counties	a,b,c, e,f,g,h
Borch and Johnsen 1982 (abstract only)	Three generations of Danish men (Born 1894-1903, 1904-1923)	Lung cancer incidence	Residence in Copenhagen compared to the rural areas of the country	Cigarette, pipe, and cigar smoking (based on amount smoked)	Difference in smoking habits insufficient to explain all of the excess lung cancer risk. The risk ratio in Copenhagen compared to Danish rural areas is 1.10-1.40. When smoking habits of the 1914-1923 and the 1894-1903 birth cohorts are taken into account, the risk ratio increases to 1.5-2.4.	a,c,d f

*See code to comments, p. A-1

TABLE II-1. URBAN-RURAL AND OTHER GEOGRAPHIC STUDIES OF CANCER:
A. ECOLOGIC STUDIES (Continued)

Author/Date	Population	Sites Investigated	Risk Indicator	Other Variables	Principal Findings	Comments*
Bozzo et al. 1979	White; male/female; U.S. counties	Malignant neoplasms; respiratory, digestive, urinary tract neoplasms	Logarithm of estimated SO_2 emissions in tons/sq mile, 1970	Median family income; population mobility	Positive correlation between pollution and outmigration. Findings show age-specific and non-site-specific association with malignant neoplasms	b,c,f, g,h
Carnow and Meier 1973	White/nonwhite; male/female; 48 contiguous states	Pulmonary cancer mortality rates, 1969	Weighted averages of benzo[a]pyrene in ambient air	Cigarette sales/person over 15 years of age	Increase of 1 µg benzo[a]-pyrene as pollution index related to 5% increase in pulmonary cancer death rate	a,b,c e,f,g,h
	White/nonwhite; male; 19 North American and European countries	Pulmonary cancer mortality rates, 1958-1959	Solid fuel consumption per capita, in metric tons/persons/year, 1955-1958	Cigarette consumption per capita, in thousands of cigarettes/person over 15 years of age	Increase of 1 metric ton of coal burned per capita was related to 20% increase in male lung cancer deaths	
Demopoulos and Gutman 1980	White; males; 5 Eastern states	Total cancer mortality rates, 1950-1969	Percentage of male workforce employed in "heavy" industry; percentage state population residing in areas with heavy industry	Urban density	No relationship between total white male cancer mortality rates and either pollution variable. Conclusion: Urban density is most significant factor in accounting for New Jersey's elevated cancer rates	a,b,c d,e,f, g,h

*See code to comments, p. A-1

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TABLE II-1. URBAN-RURAL AND OTHER GEOGRAPHIC STUDIES OF CANCER: A. ECOLOGIC STUDIES (Continued)

Author/Date	Population	Sites Investigated	Risk Indicator	Other Variables	Principal Findings	Comments*
Demopoulos and Gutman 1980 (cont'd.)	White/nonwhite; male; 7 U.S. cities	Incidence of cancers of lung, nasopharynx, stomach and all cancers for years 1969-1971	Subjective designation of cities as "Clean" or "Dirty"	No. of males employed in heavy industry	Average cancer incidence rates higher in "clean" than in "dirty" cities	
Ford and Bialik 1980	U.S. adults (aged 45 or older), 1969-1971	Cancer mortality for 7 sites and all cancer	Residence in one of 3 categories: metropolitan counties with central cities, metropolitan counties without central cities, and nonmetropolitan counties	Age, race, and sex	For the U.S. adult population, 84% of cancer mortality appears to be related to the degree of urbanization; this correlation applies separately to men, women, whites, and nonwhites as well as to the total population	a,b,c, d,e,f, g
	Adults (aged 45 or older) in Cuyahoga County, Ohio, 1969-1971	Cancer mortality for 5 sites and all cancer	Residence in one of 4 urban zones of decreasing air pollution as measured by SO_2, particulates, or NO_2 or in a suburban zone of presumed low pollution	Socioeconomic indicators; poverty, unemployment, income, education; migration; race; age; and sex	Respiratory cancer was correlated with general air pollution characteristics, but other cancer mortality was correlated with socioeconomic status; high migration was correlated with low cancer rates	a,b,c, f,g
Greenberg 1979	White/Nonwhite; Male/Female; 49 counties comprising New Jersey-Philadelphia metropolitan region	Stomach; large intestine, rectum, liver, pancreas, lung, breast, prostate, kidney, bladder, skin; leukemia; all cancers for 1950-1969	Total suspended particulates (μg/m^3) for 1953-1957 and 1972-1975, transformed to take into account wind direction and distance from source Tons of coal equivalent burned by electric power plants. Ten air pollution indices were developed	14 personal environmental factors, 33 occupational variables, 2 water pollution indicators, 3 variables created by factor analysis	White male and female lung cancer mortality rates strongly associated with various measures of air pollution, presence of chemical and transportation equipment industries, and Polish and Italian populations	a,b,e, f,g,h

TABLE II-1. URBAN-RURAL AND OTHER GEOGRAPHIC STUDIES OF CANCER:
A. ECOLOGIC STUDIES (Continued)

Author/Date	Population	Sites Investigated	Risk Indicator	Other Variables	Principal Findings	Comments*
Henderson et al. 1975	White; male/female; 1586 census tracts in Los Angeles County	Cancer of lung, oral cavity, pancreas, larynx, and bladder, 1968-1972	Ambient levels of polynuclear aromatic hydrocarbons (PAH)	Social class index based on average educational level and median family income	Increased rate of lung cancer among males in south central Los Angeles. Excess risk occurs across several social classes and occupational categories. Geographic distribution of lung cancer cases correlated with the general location of industries emitting PAH's (See Pike et al. 1979)	a,b,c e,f,g, h
Hoover and Fraumeni 1975	White/nonwhite; male/female; 139 U.S. counties in which the chemical industry is most highly concentrated	Cancers of lung, bladder, liver and gallbladder, nasal sinuses, larynx, skin, bone, uterine cervix, leukemia, malignant melanoma, and total cancer	Estimated no. of workers/county engaged in chemical production	Percent urbanization; median school years; median family income; percent unemployed; employment in other manufacturing units	Mortality rates for cancer of the lung, liver, bladder and certain other cancers significantly higher in counties where chemical industry is most concentrated. This could not be explained by confounding variables such as urbanization, SES, or employment in non-chemical industries. For lung cancer, positive gradients associated with manufacture of industrial gases, pharmaceuticals, soaps, paints, synthetic rubber	a,b,c e,f,g, h

*See code to comments, p. A-1

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TABLE II-1. URBAN-RURAL AND OTHER GEOGRAPHIC STUDIES OF CANCER: A. ECOLOGIC STUDIES (Continued)

Author/Date	Population	Sites Investigated	Risk Indicator	Other Variables	Principal Findings	Comments*
Hoover et al. 1975	White male/female; 957 counties listed as 100% rural, 13 counties as 100% urban in 1960 census	35 cancer sites, 1950-1969	Urban vs. rural	None	Mortality rates for most types of cancer were higher in urban areas. In particular, U/R ratio for lung cancer was 1.89 (M) and 1.64 (F)	a,b,c, d,e,f, g,h
	White; male/female; 2,086 remaining U.S. counties		Urban vs. rural	Social class (median years of schooling for adult population)	For some types of cancer, social class and urbanizaton are correlated	
Lave and Seskin 1977	White/nonwhite; male/female; 117 SMSA's	Buccal and pharyngeal, digestive, respiratory, breast, and total cancer, 1960 and 1961	Minimum, mean and maximum levels of sulfates and suspended particulates	Percentage of population older than 65 years; population density, occupation mix; climate; home heating characteristics	For total cancers and cancer of digestive system, significant correlation with air pollution in 1960 and 1961	a,b,e, f,g,h
Levin et al. 1960	All races; male/female; New York State (exclusive of New York City)	Cancer incidence rates for 18 sites, 1949, 1951	Urban/rural	None	For lung cancer, ratios of urban to rural rates are greater than one for both males (1.41) and females (1.07). Urban/rural ratios for nonmetropolitan counties much greater than metropolitan counties	a,b,c, d,e,f, g,h

*See code to comments, p. A-1

TABLE II-1. URBAN-RURAL AND OTHER GEOGRAPHIC STUDIES OF CANCER:
A. ECOLOGIC STUDIES (Continued)

Author/Date	Population	Sites Investigated	Risk Indicator	Other Variables	Principal Findings	Comments*
MacDonald 1976	White/nonwhite/ Spanish surnamed; male/ female; 15 regions within city of Houston, Tex.	Mortality rates for total malignant respiratory and total cancer, 1940-1969	Presence of industry	None	Gradient for lung cancer follows the southeast-northwest wind gradient. Also, a general though not completely consistent relationship between number of industrial facilities and respiratory cancer	a,b,c, d,e,f, g,h
Menck et al. 1974	White; male/ female; 26 health districts in Los Angeles County	Lung cancer mortality, 1968-1969	Polynuclear aromatic hydrocarbons (PAH) in air and and soil	Socioeconomic status (index based on average income and educational level)	A 40% increase in lung cancer mortality rates among males living in certain heavily industrialized areas of Los Angeles County relative to surrounding sections of county. Areas characterized by high concentrations of PAH's	b,c,e, f,g,h
Prindle 1959	White; male/ female; 163 metropolitan areas in the U.S.	Cancer of lung, bronchus, and trachea, cancer of esophagus and stomach; 1950 mortality data	Urbanization, fuel consumption (all fuel, gas, coal home heating units, service station sales)	Population density, city size	A twofold difference in respiratory cancer between urban and rural areas; smoking differences unlikely to account for urban excess. Moderate correlations between respiratory,	a,b,c, d,e,f, g,h

*See code to comments, p. A-1

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TABLE II-1. URBAN-RURAL AND OTHER GEOGRAPHIC STUDIES OF CANCER:
A. ECOLOGIC STUDIES (Continued)

Author/Date	Population	Sites Investigated	Risk Indicator	Other Variables	Principal Findings	Comments*
Prindle 1959 (cont'd.)					stomach, and esophageal cancer, and various fuel consumption indices, were observed. Conclusion: Insufficient data to support causal association between these diseases and air pollution	
Robertson 1980	All races; male/female; 98 U.S. cities	Total cancer, 1970 mortality data	Motor vehicles/ sq. mile and percent adults employed as production workers	Percent population in county in 1965; heating degree days; population density; 10 water quality variables	Motor vehicle density, percent population residing in county in 1965, percent adults employed as production workers, barium in water supply, and climate found to explain more than half the intercity variation in cancer mortality. Motor vehicle density highly correlated with population density	a,b,d e,f
Stocks 1960	All races; male/female; 26 areas of Northern England	Cancer of lung, stomach, breast (F); mortality rates, 1950-53	Air concentrations of 4 polynuclear aromatic hydrocarbons, smoke, and 13 trace elements	Population density; percent male age 15 and over in social classes IV and/or V	Lung cancer mortality (M) strongly correlated with smoke density, 3:4 benzopyrene, beryllium, molybdenum, arsenic, zinc, and vanadium	b,c,e f,g,h

*See code to comments, p. A-1

TABLE II-1. URBAN-RURAL AND OTHER GEOGRAPHIC STUDIES OF CANCER:
A. ECOLOGIC STUDIES (Continued)

Author/Date	Population	Sites Investigated	Risk Indicator	Other Variables	Principal Findings	Comments*
Stocks 1960 (Cont'd.)	All races; male/female; 45 districts of Lancashire and West Riding of Yorkshire	Same as above	Air concentrations of smoke and atmospheric deposit	Same as above	Lung cancer mortality (M and F) strongly correlated with smoke density in ambient air. Lung (M and F) and stomach (F) cancers also strongly associated with atmospheric deposits	
	All races; male/female; 30 county boroughs in England	Same as above	Air concentrations of smoke	Same as above	Lung cancer mortality strongly correlated with smoke density. Cancers of stomach and intestines (M and F) also significantly correlated with smoke density when social factors taken into account	
Stocks 1966	All races; male/female; 8 European areas	Lung cancer mortality rates 1958-1962	Smoke density; ambient air levels of 4 polynuclear aromatic hydrocarbons and 7 trace elements (1-year sampling during various periods 1953-1963)	Cigarette consumption (based on population surveys undertaken at various times, 1951-1963)	Smoking and air pollution significantly correlated with lung cancer mortality rates in 8 European areas	c,d,e,f,g,h

*See code to comments, p. A-1

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TABLE II-1. URBAN-RURAL AND OTHER GEOGRAPHIC STUDIES OF CANCER: A. ECOLOGIC STUDIES (Continued)

Author/Date	Population	Sites Investigated	Risk Indicator	Other Variables	Principal Findings	Comments*
Stocks 1966 (Cont'd.)	All races; male/female; 19 countries	Lung cancer mortality rates 1958-1959	Solid fuel consumption and liquid fuel consumption (1951-1952	Cigarette consumption	Significant correlations between lung cancer mortality and both cigarette and solid fuel consumption. No such correlations between lung cancer mortality and liquid fuel consumption	a,c,d, e,f,g, h
Weinberg et al. 1982	White males, 35 or older, in a high risk area (Lawrenceville) compared to a low risk area (South Hills) of Allegheny County, Pennsylvania	Lung cancer mortality in white males, 1969-1971	Residence in the Lawrenceville area of Pittsburgh	Smoking habits determined by sampling current residents of the high and low risk areas; relative risks for smokers assumed to be 21 in the high risk area and 14 in the low risk area are unusually high	The high risk area had a significantly greater proportion of males currently smoking and who had ever smoked compared to the low risk area; the high risk area also had an average age at starting over 4 years earlier and proportionately fewer smokers of filter cigarettes. Calculations of attributable risks based on presumed relative risks led to 82.7% of lung cancers related to smoking in the low risk area and 91.2% in the high risk area	a,c,f, g
Weiss 1978	White; male/female (age 30 and over); 10 health districts in Philadelphia	Lung cancer mortality rates, 1968-1972	Settled dust (equiv. tons of particulate matter deposited/sq. mile/month) and sulfation rate (mg SO_3/100 cm^2/day) in 1960	None	Geographical distribution of lung cancer similar to distribution of the two air pollution variables. Ratios of male to female lung cancer mortality highest in most industrialized sectors of city	b,c,d, e,f,g, h
Winklestein et al. 1967	White; male, 50 years and older; Buffalo and Erie County	Lung cancer mortality rates, 1959-1961	Suspended particulates (geometric means μg/cu. cm/24 hr.) July 1961-June 1963	Median income of census tract of residence	For lung and bronchial cancer, no significant differences in rates between areas of high air pollution and low air pollution	b,c,e, f,g,h

*See code to comments, p. A-1

TABLE II-1. URBAN-RURAL AND OTHER GEOGRAPHIC STUDIES OF CANCER:
A. ECOLOGIC STUDIES (Concluded)

Author/Date	Population	Sites Investigated	Risk Indicator	Other Variables	Principal Findings	Comments*
Zeidberg et al. 1967	White/nonwhite; male/female; Nashville, Tenn.	Lung cancer mortality rates, 1949-1960	Sulfation (SO_3), dustfall, soiling index, and 24-hour SO_2	Socioeconomic status (based on median occupational level, median family income, median years of schooling, percentage of houses with greater than 1.01 persons/room)	For lung and bronchial cancer, no significant difference in rates between areas of high air pollution and low air pollution	b,c,e, f,g,h

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*See code to comments, p. A-1

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TABLE II-1. URBAN-RURAL AND OTHER GEOGRAPHIC STUDIES OF CANCER:
B. COHORT STUDIES

Author/Date	Population	Sites Investigated	Risk Indicator	Other Variables	Principal Findings	Comments*
Buell et al. 1967	Males; members of California Division, American Legion	Lung cancer	Residence (Los Angeles County, San Francisco Bay Area, San Diego Counties, and all other California Counties)	Smoking, occupational history, duration of residence	With controls for smoking and duration of residence, risk of lung cancer in metropolitan areas was 2.5-3.9 times higher than in rural areas of California. However, rate for Los Angeles County, where photochemical air pollution levels are highest, was not greater than other major metropolitan areas	a,f
Cederlof et al. 1975	All races; male/female; residents of Sweden	Lung cancer	Residence (cities, smaller towns, rural)	Smoking habits, income	Lung cancer more common among male smokers residing in large cities (Stockholm, Gothenburg, or Malmo) than in smaller towns and rural areas. Similar trend among women smokers but based on small number of cases	a,c,e,f

*See code to comments, p. A-1

TABLE II-1 - URBAN-RURAL AND OTHER GEOGRAPHIC STUDIES OF CANCER:
B. COHORT STUDIES (Concluded)

Author/Date	Population	Sites Investigated	Risk Indicator	Other Variables	Principal Findings	Comments*
Hammond and Horn 1958	White; males; 187,783 men from 394 counties in 9 states	Lung cancer	Place of residence (city of 50,000+, city of 10-50,000, suburb or town, rural)	Smoking habits	Strong association between cigarette smoking and cancers of lung, larynx, and esophagus. With smoking habts taken into consideration, lung cancer death rates were somewhat higher in cities than in rural areas	a,c,d,e,f
Hammond and Garfinkel 1980	All races; male/female; 1;078,894 residents from 1,121 counties in 25 states	Lung cancer	Place of residence (metropolitan areas of >1,000,000, metropolitan areas of ≤1,000,000 and nonmetropolitan areas)	Smoking habits	Strong association between cigarette smoking and lung cancer. With smoking habits taken into consideration, male lung cancer rates higher in cities than in rural areas. Male lung cancer rates also increased with size of metropolitan area; this increase more rapid for men occupationally exposed to dust, fumes, etc., suggesting some interaction	a,d,e,f
Stocks and Campbell 1955	All races; male; male residents (age 45-74) who died of lung cancer, mid-1952 to mid-1954, northwest England and Wales	Lung cancer	Ambient levels of total smoke, trace elements, benzo-[a]pyrene, and other polynuclear aromatic hydrocarbons (PAH)	Smoking	Lung cancer mortality rates increased with number of cigarettes smoked/week. Liverpool rates exceeded rural rates in every smoking category, but urban/rural ratio falls progressively from about 9/1 among nonsmokers to near unity for heavy smokers. Absolute urban excess remains fairly constant in each smoking category, suggesting that effects of air pollution are additive with smoking. Estimated that 3/8 of urban excess is due to air pollution	a,d,e,f

*See code to comments, p. A-1

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TABLE II-1 - URBAN-RURAL AND OTHER GEOGRAPHIC STUDIES OF CANCER: C. CASE-CONTROL STUDIES

Author/ Date	Study Population	Control Population	Sites Investigated	Risk Variable	Other Variables	Principal Findings	Comments*
Dean 1966	All races; male/female; all N. Ireland residents aged 35 years or older who died of lung cancer or bronchitis, 1960-1962	Next person in Register of Deaths of same sex in same 5-year age group, who resided in the same type of area, and who died of a nonrespiratory illness	Lung cancer	Place of residence	Smoking habits, social class	For males and females, lung cancer rates in Belfast ranged from 1.8 to 5.5 times those in truly rural districts; evident for all categories of smoking. At intermediate levels of urbanization several inconsistencies in these patterns. Strong association between smoking and lung cancer also observed	a,c,e,f
Dean et al. 1977, 1978	Cases and controls aged 35 or older from Cleveland County in northeast England, including males and females, 1963-1972		Lung cancer mortality	Residence in the Eston or Stockton sections; the Eston and Stockton areas were also subdivided into areas of high, medium and low pollution based on measurements in the study area, 1963-1972, of SO_2, "smoke," insoluble particles and ferricoxide	Smoking (amount smoked, age at starting, type of cigarette or cigar, degree of inhalation, and duration of smoking); social class; exposure to dust on the job and type of dusty job; exposure to fumes on the job	After adjusting for age, smoking and social class, sizable relative risks of lung cancer remained in both the Eston and Stockton areas compared to rural areas (1.65-2.17 in men, 1.20-1.78 in women). This excess occurred in all smoking categories. The lung cancer rates among smokers of various categories increased over time (1952-1962 to 1963-1972). Smoking filter cigarettes carries a lower risk than smoking nonfilter cigarettes.	a,e,f,g

TABLE II-1. URBAN-RURAL AND OTHER GEOGRAPHIC STUDIES OF CANCER: C. CASE-CONTROL STUDIES (Continued)

Author/ Date	Study Population	Control Population	Sites Investigated	Risk Variable	Other Variables	Principal Findings	Comments*
Haenszel et al. 1962	White; males; 10% sample of all white male lung cancer deaths in U.S. during 1958	Lung cancer	Place and duration of residence	Smoking history		Strong smoking class gradient in lung cancer mortality. Ratio of urban lung cancer to rural rates showed consistent increase with duration of residence when adjusted for age and smoking history. However, absolute rates for urban and rural areas declined with increasing duration of residence. Joint effects of residence and smoking on lung cancer rates much greater than that expected on assumption of additivity of effects.	a,c,d, f,h
Haenszel and Tauber 1964	White; female; 10% sample of all white female lung cancer deaths in U.S. during 1958 and 1959 (683 women)		Lung cancer	Place and duration of residence	Smoking history	As with males, strong smoking class gradient in lung cancer. However, male smokers of 1 pack or less/day and more than 1 pack had lung cancer rates 4 times greater than corresponding female rates. Urban/rural ratios showed consistent increase with duration of residence though absolute rates for urban and rural areas declined with increasing duration of residence.	a,c,d,e, f

*See code to comments, p. A-1

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TABLE II-1. URBAN-RURAL AND OTHER GEOGRAPHIC STUDIES OF CANCER:
C. CASE-CONTROL STUDIES (Continued)

Author/ Date	Study Population	Control Population	Sites Investigated	Risk Variable	Other Variables	Principal Findings	Comments*
Hitosugi 1968	Japanese; Male/female; all lung cancer cases in Amagaski and Nishinomiya, 1958-1965	Random sample of 2241 males and 2475 females age 35-74 years from the two cities	Lung cancer	Place of residence classified according to degree of pollution (dustfall, SO_2, suspended particulates, trace elements, and aromatic hydrocarbons)	Smoking history	Significantly higher lung cancer mortality rates among smokers in each category of air pollution. Mortality rate for lung cancer increased slightly with increase in air pollution among smokers, but not among nonsmokers	a,c,d,f

*See code to comments, p. A-1

TABLE II-1. URBAN-RURAL AND OTHER GEOGRAPHIC STUDIES OF CANCER:
C. CASE-CONTROL STUDIES (Concluded)

Author/ Date	Study Population	Control Population	Sites Investigated	Risk Variable	Other Variables	Principal Findings	Comments*
Pike et al. 1979	White; Male/female; 955 newly diagnosed lung cancer patients (1972-1975) residing in central south Los Angeles County	Controls of same sex, race, and 5-year age group randomly selected from 173 census tracts in central south Los Angeles County; second control group was 1270 (893 males, 377 females) newly diagnosed lung cancer patients (1972-1973) from remainder of Los Angeles County	Lung cancer	Residence in central south Los Angeles County (polynuclear aromatic hydrocarbons)	Occupation (white- vs. blue-collar and 11 occupational categories, U.S. Census code); smoking habits; duration of residence	No association between long-term residence and risk of lung cancer. Occupational differences appear to be explanation for localized increased rate of lung cancer	a,f
Vena 1982	White males, Erie County, New York 1957-1965		Lung cancer mortality	Residence in a high to medium pollution area determined by 1960 measurements and historical review of problem point sources	Cigarette smoking (amount and duration); occupation in one of 32 high-risk categories	Apparent synergistic relationship between smoking and air pollution and smoking and occupation. For individuals born after 1900, air pollution, occupation, and smoking and all combinations are significant risk factors. Although the overall findings do not support the hypothesis that air pollution alone is a significant risk factor, the study indicates that air pollution should not be dismissed as a risk factor	a,f,g

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*See code to comments, p. A-1

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APPENDIX B

TABLE III-1

CONCENTRATIONS OF SUSPECTED OR KNOWN CARCINOGENIC SUBSTANCES IN THE AIR

Substance	References Establishing Carcinogenicity	Source of Sample	Concentration	Reference Indicating Concentration
ACRYLONITRILE	IARC 1979a (rats)	Industrial emissions	0.1-325 μg/m^3	USEPA 1979b
AZA-HETEROCYCLIC COMPOUNDS				
Benzo[c]-acridine	Hakim 1968 (rats, mice)	Particles	0-15 μg/ 1,000 m^3	Stanley et al. 1968
		Urban air	0.6 μg/ 1,000 m^3	Sawicki et al. 1965c
		Urban air	1 μg/ 1,000 m^3	Shubik et al. 1970
		Vehicle exhaust	200 μg/ 1,000 m^3	Sawicki et al. 1965b
Dibenz[a,h]-acridine	Badger et al. 1940 (mice); Andervont and Shimkin 1940 (mice)	Urban air	0.08 μg/ 1,000 m^3	Sawicki et al. 1965c
		Urban air	0.2 μg/ 1,000 m^3	Shubik et al. 1970
		Vehicle exhaust	Present	Sawicki et al. 1965b

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TABLE III-1 (continued)

CONCENTRATIONS OF SUSPECTED OR KNOWN CARCINOGENIC SUBSTANCES IN THE AIR

Substance	Carcinogenicity	References of Sample	Establishing Concentration	Source Concentration
AZA-HETEROCYCLIC COMPOUNDS (Continued)				
	Dibenz[a,j]-acridine	Wynder and Hoffman 1963 (mice); Badger et al. 1940 (mice); Andervont and Shimkin 1940 (mice)	exhaust	Urban air Vehicle
BENZENE	IARC 1974b (humans);	Urban air Infante et al. 1977 (humans); Ott et al. 1978 (humans)	5-90 µg/	NAS 1976
			Urban air	2-40 ppb
			Urban air	30-40 µg/m^3
CARBON TETRA-CHLORIDE	Della Porta et al. 1961 (hamsters); NCI 1976	Urban air (rats)	0.87-9.1 µg/m^3	Ohta et al. 1976, Singh et al. 1976
			Industrial	38 µg/m^3

TABLE III-1 (continued)

CONCENTRATIONS OF SUSPECTED OR KNOWN CARCINOGENIC SUBSTANCES IN THE AIR

Substance	References Establishing Carcinogenicity	Source of Sample	Concentration	Reference Indicating Concentration
CHLOROFORM	Eschenbrenner 1945 (mice); NCI 1976 (mice, rats)	Urban air	0.01-15 ppb	Lillian et al. 1975
EPICHLOROHYDRIN	IARC 1976 (mice)	Industrial emissions	0.001-50 $\mu g/m^3$	USEPA 1980
ETHYLENE DIBROMIDE	NCI 1978b (mice, rats); Olson et al. 1973 (mice, rats)	Industrial emissions	0.069-0.33 $\mu g/m^3$	USEPA 1975, USEPA 1979b
ETHYLENE OXIDE	IARC 1976 (rats)	Industrial emissions	0.0005-10 $\mu g/m^3$	USEPA 1980
FORMALDEHYDE	Watanabe et al. 1954 (rats); CIIT 1980 (rats)	Industrial emissions	0.01-2500 $\mu g/m^3$	Cleveland et al. 1977, Tuazon et al. 1978, USEPA 1980

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TABLE III-1 (continued)

CONCENTRATIONS OF SUSPECTED OR KNOWN CARCINOGENIC SUBSTANCES IN THE AIR

Substance	References Establishing Carcinogenicity	Source of Sample	Concentration	Reference Indicating Concentration
HALOGENATED PESTICIDES				
DDT	IARC 1974a (mice); Rossi et al. 1977 (rats)	Rural air	0.1-1.3 ng/m^3	Tabor 1966
		Residential air	500 μg/m^3	Jegier 1969
		Ocean air	0.01-.09 ng/m^3	Bidleman and Olney 1974
		Rural air	8.0-417.0 ng/m^3	Stanley et al. 1971
		Urban air	0.5-1.0 ng/m^3	Stanley et al. 1971
Dieldrin	IARC 1974a (mice)	Urban air	1.2-27.2 ng/m^3	Stanley et al. 1971
		Air	0.8-3.4 ng/m^3	Yobs et al. 1972
Lindane	Thorpe and Walker 1973 (mice); Ito et al. 1973 (mice)	Rural air	0.4-1.4 ng/m^3	Stanley et al. 1971

TABLE III-1 (continued)

CONCENTRATIONS OF SUSPECTED OR KNOWN CARCINOGENIC SUBSTANCES IN THE AIR

Substance	References Establishing Carcinogenicity	Source of Sample	Concentration	Reference Indicating Concentration
HALOGENATED PESTICIDES (Continued)				
Chlordane	NCI 1977a (mice)	Rural air	0.6-1.9 ng/m^3	Tabor 1966
		Urban air	0.25 ng/m^3	Bidleman and Olney 1974
		Ocean air	0.005-0.17 ng/m^3	Bidleman and Olney 1974
INORGANIC PARTICULATES AND GASES				
Arsenic	IARC 1980 (humans)	Industrial emissions	0-2.5 μg/m^3	IARC 1980, Suta 1978
		Urban air	<1-14 ng/m^3	KVB 1980
Asbestos	Wagner 1972 (rats); IARC 1977 (rats, mice, hamsters, rabbits, humans)	Industrial emissions	0.1-100 μg/ 1,000 m^3	Nicholson and Pundsack 1973
		Desert air	3-53 x 10^4 fibers/m^3	Cooper et al. 1979
		Urban air	3,500-5,700 fibers/m^3	Murchio et al. 1973
		Urban air	7-10 x 10^5 fibers/m^3	Wesolowski 1975
		Urban air	4-10 x 10^5 fibers/m^3	KVB 1980

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TABLE III-1 (continued)

CONCENTRATIONS OF SUSPECTED OR KNOWN CARCINOGENIC SUBSTANCES IN THE AIR

Substance	References Establishing Carcinogenicity	Source of Sample	Concentration	Reference Indicating Concentration
INORGANIC PARTICULATES AND GASES (Continued)				
Beryllium	IARC 1980 (rats, rabbits monkeys)	Industrial emissions	0.003-19.5 µg/m^3	IARC 1980
Cadmium	IARC 1976 (rats, mice); Althouse et al. 1980 (humans)	Industrial emissions	0.04-0.25 µg/m^3	Friberg and Cederlof 1978
Chromium	IARC 1980 (rats, humans)	Industrial emissions	0.01-21.5 µg/m^3	IARC 1980
Lead	IARC 1980 (mice, rats)	Industrial emissions, auto emissions	0.4-7.4 µg/m^3 (average, 1.1)	IARC 1980
		Smelter emissions	6.67-2990 µg/m^3	
Nickel	IARC 1976 (mice, rats, hamsters)	Industrial emissions	0.00769-15.8 µg/m^3	USEPA 1980

TABLE III-1 (continued)

CONCENTRATIONS OF SUSPECTED OR KNOWN CARCINOGENIC SUBSTANCES IN THE AIR

Substance	References Establishing Carcinogenicity	Source of Sample	Concentration	Reference Indicating Concentration
N-NITROSO COMPOUNDS	IARC 1978 (8 species)	Industrial effluents	1-36 $\mu g/m^3$	Fine et al. 1977
		Urban air	1-40 ng/m^3	Fine et al. 1977
		Air	0.03-1.0 $\mu g/m^3$	Gordon 1978
		Urban air	<0.03-0.48 $\mu g/m^3$	KVB 1980
POLYCYCLIC AROMATIC HYDROCARBONS				
Benzo[a]pyrene	IARC 1973b (9 species); Laskin et al. 1970 (rats); Saffiotti et al. 1972a (hamsters); Noyes 1969 (primates); Crocker et al. 1970 (primates); Bryan and Shimkin 1943 (mice)	Urban air	1.8-61 $\mu g/1{,}000\ m^3$	Kotin and Falk 1964
		Rural air	0.01-1.9 $\mu g/1{,}000\ m^3$	Kotin and Falk 1964
		Vehicle exhaust	122-227 ppm (of total extract)	Sullivan and Cleary 1964
		Urban air	1.04 $\mu g/m^3$	King et al. 1977
		Air	0.01-100 $\mu g/1{,}000\ m^3$	Shubik et al. 1970
		Urban air 1966-1977	1-5$\mu g/1{,}000\ m^3$	CEQ 1980

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TABLE III-1 (continued)

CONCENTRATIONS OF SUSPECTED OR KNOWN CARCINOGENIC SUBSTANCES IN THE AIR

Substance	References Establishing Carcinogenicity	Source of Sample	Concentration	Reference Indicating Concentration
POLYCYCLIC AROMATIC HYDROCARBONS (Continued)				
Dibenz[a,h]-anthracene	Bryan and Shimkin 1943 (mice); Wynder and Hoffman 1959a (mice); O'Gara et al. 1965 (mice)	Urban dust	3.2-32 μg/ 1,000 m^3	Grimmer 1968
Benzo[j]-fluoranthene	Wynder and Hoffman 1959b (mice)	Vehicle exhaust	Present	Hoffman and Wynder 1962
Dibenzo[a,i]-pyrene	Wodinsky et al. 1964 (hamsters); Epstein 1967 (mice)	Vehicle exhaust	Present	Hoffman and Wynder 1962
Benzo[e]pyrene	Wynder and Hoffman 1959a (mice)	Air	0.01-208 μg/ 1,000 m^3	IARC 1973b
		Airborne particulates	180-570 μg/g (of total extract)	Epstein et al. 1966

TABLE III-1 (continued)

CONCENTRATIONS OF SUSPECTED OR KNOWN CARCINOGENIC SUBSTANCES IN THE AIR

Substance	References Establishing Carcinogenicity	Source of Sample	Concentration	Reference Indicating Concentration
POLYCYCLIC AROMATIC HYDROCARBONS (Continued)				
Benz[a]-anthracene	Klein 1963 (mice); Bingham and Falk 1969 (mice)	Urban air	0.6-13.7 μg/ 1,000 m^3	IARC 1973b
		Airborne particulates	43-280 μg/g (of total extract)	Epstein et al. 1966
		Industrial effluents	Present	Sawicki et al. 1965a
Dibenzo[a,e]-pyrene	Hoffman and Wynder 1966 (mice)	Vehicle exhaust	Present	Lyons 1959
Chrysene	Boyland and Sims 1967 (mice); Wynder and Hoffman 1959a (mice)	Urban air	1.8-13.3 μg/ 1,000 m^3	Cleary 1963
		Airborne particulates	150-490 μg/g (of total extract)	Epstein et al. 1966

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TABLE III-1 (continued)

CONCENTRATIONS OF SUSPECTED OR KNOWN CARCINOGENIC SUBSTANCES IN THE AIR

Substance	References Establishing Carcinogenicity	Source of Sample	Concentration	Reference Indicating Concentration
POLYCHLORINATED BIPHENYLS	Ito et al. 1973 (mice); Kimbrough and Linder 1974 (mice); Kimbrough et al. 1975 (rats); NCI 1978a (rats)	Urban air	0.5-36 ng/m^3	NAS 1979
		Rural air	0.002-.07 ng/m^3	NAS 1979
RADIONUCLIDES	NAS 1972c (several species)	Urban air	2 x 10^{-10} Ci/m^3	Natusch 1978
TETRACHLORO-ETHYLENE	NCI 1977b (mice)	Los Angeles air	1.25 ppb average, 4.2 ppb maximum	Simmonds et al. 1974
		Urban air	0.18-4.2 ppb	Lillian et al. 1975
		Rural air	0.07 ppb	Lillian et al. 1975
TCDD	Kociba et al. 1978 (rats)	Kiln effluent	2.8-8.2 ppm	Dow 1978
		Incinerator and boiler effluents	0.1-0.6 ppm	Buser et al. 1978

TABLE III-1 (concluded)

CONCENTRATIONS OF SUSPECTED OR KNOWN CARCINOGENIC SUBSTANCES IN THE AIR

Substance	References Establishing Carcinogenicity	Source of Sample	Concentration	Reference Indicating Concentration
TRICHLOROETHYLENE	NCI 1976 (mice)	Air	11 ng/m^3	McConnell et al. 1975
VINYL CHLORIDE	IARC 1979a (mice, rats hamsters, humans)	Industrial emissions	2.6-5.2 ng/m^3	USEPA 1974
		Urban air	38.5-790 ppb	Lillian et al. 1975
VINYLIDENE CHLORIDE	Maltoni et al. 1977 (mice)	Air from towns with factories	0.04-100 ng/m^3	RTI 1977

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APPENDIX C

CALCULATION OF THE AGE-ADJUSTED LUNG CANCER RATES IN MALES AND IN THE GENERAL POPULATION

According to the U.S. Bureau of the Census (1980), the proportion of whites in the U.S. population in 1975 was 86.9%, and for blacks the proportion was 11.5%, with 1.6% unclassified. The proportion of males was 48.7%, and 51.3% of the population was female. Pollack and Horm (1980) provided sex-specific rates of lung cancer mortality per 10^5 persons, age adjusted to the 1970 U.S. population, which are:

	Males	Females
Whites	64.8	15.5
Blacks	80.5	15.2

So for the male population, the rate of lung cancer mortality per 10^5 persons is:

$$\frac{(64.8)(.869) + (80.5)(.115)}{(.984)} = 67$$

For the general population, it is:

$$\frac{(.487)[(64.8)(.869)+(80.5)(.115)]+(.513)[(15.5)(.869)+(15.2)(.115)]}{(.984)}$$

$$= 40$$

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APPENDIX D

CALCULATION OF THE RISK OF LUNG CANCER TO THE GENERAL POPULATION AS A PROPORTION OF THE RISK TO MALES

The risk of lung cancer mortality per ng/m^3 of benzo[a]-pyrene estimated by Pike et al. (1975) based on the data of Stocks (1958) is 1.4 deaths/10^5 persons among smokers and 0.4 deaths/10^5 persons among nonsmokers. As discussed in Chapter II, the magnitude of these risks per unit exposure are likely to be underestimated, but the relative difference in risk of 3.5 (1.4/0.4) is probably reliable and is reported by Wilson et al. (1980) as statistically significant. Because a number of estimates were made for the risk of lung cancer mortality among males only, it was necessary to derive the risk to the general population as a function of risk in males.

DHEW (1979) provided data on smoking habits in men and women in 1977: 40% of men and 30% of women are smokers. (This represents a decline in previous smoking habits.) The recent data of Hammond and Seidman (1980) indicate that the relative risk of lung cancer mortality among smokers is 8.53 in men and 3.58 in women. We assume that the excess risk from air pollution is proportionately the same (8.53/3.58 = 2.4). So if the relative risk among male smokers is 3.5, the risk in females will be 2.05 (1 + 1/2.4 x 2.5); we assume that the risk among nonsmokers is the same in males and females (i.e., 1.0). From the census data (U.S. Bureau of the Census 1980),

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the fraction of the population that is male is 0.487, and the fraction of the population that is female is 0.513. Thus,

$$(0.487)\ [(3.5)\ (0.4) + (1)\ (0.6)] +$$
$$(0.513)\ [(2.05)\ (0.3) + (1)\ (0.7)] = 1.65$$

The relative risk among all males is 2.0, and the relative risk in the general population is 82.4% of the risk in males (1.65/2.0).

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APPENDIX E

DERIVATION OF AN ESTIMATE OF THE PROPORTION OF LUNG CANCERS ASSOCIATED WITH THE URBAN ENVIRONMENT

In this Appendix, we derive an estimate of the proportion of lung cancers associated with the urban environment. Earlier versions of this calculation were included in our previous reports (Clement 1981, Karch and Schneiderman 1981), but these have been modified to take into account criticisms of these earlier versions and suggestions by CAG (1982) and other commentors.

Our estimate is derived from a study by Hammond and Garfinkel (1980), together with additional information from the same study presented by Goldsmith (1980). The data in these papers were standardized for age and smoking habits, and included information on (self-reported) occupational exposure. (The authors, however, did not give details of how the "corrections" were made, or of the age distribution and smoking habits of their standard population). Although the data presented by Hammond and Garfinkel (1980) were not fully described or given in the 1980 paper, they were clearly derived from data obtained in a survey sponsored by the American Cancer Society (ACS) from 1959 to 1965 (Hammond 1972). (Table 1 in Hammond and Garfinkel 1980 is identical to Table 5 in Hammond 1972.)

We used these data as reassembled in another recent paper by Goldsmith (1980). One can compare lung cancer mortality

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rates among men between urban and nonurban areas as Goldsmith did by combining some groups to form three categories: "metropolitan areas of greater than one million," "other non-rural places," and "non-metropolitan rural areas." The results of Goldsmith's (1980) reassembly are found in Table E-1. These data are plotted in Figure II-2 (above, p. II-82) and show a trend for increasing cancer mortality with greater urbanization in both occupationally exposed and nonexposed persons, after correction for smoking. The use of three residence or exposure categories in this sort of study has been questioned, but is apparently common practice. See, for example, Hitosugi (1968) and Vena (1982) who used similar categories.

These results provide a measure of the risk of death from lung cancer among males that is attributable to an urban effect, by contrasting the urban and the rural areas (i.e., by combining the first two categories in Table E-1 to compare with the third). These risk ratios derived for the ACS population can be weighted according to the proportion of the U.S. population in each category in 1970 (U.S. Bureau of the Census 1980). The attributable risk for an urban effect can then be computed.

This computation is illustrated in Tables E-2 and E-3. The residual urban effect, after correcting for smoking, is about 13% for both the occupationally exposed group of men and 12% for the nonoccupationally exposed group of men. This corresponds to a previously computed risk of 8.2 lung cancer

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TABLE E-1

LUNG CANCER DEATHS AMONG MEN BY PLACE OF RESIDENCE AND OCCUPATIONAL EXPOSURES--SMOKING ADJUSTED--1959-1965*

	Occupationally Exposed			Not Exposed		
	Observed	Expected	Ratio	Observed	Expected	Ratio
TOTAL	576	530.5	1.09	934	979.7	0.96
			Chi sq.=6.03, p<0.02			
Metropolitan area city (1,000,000+)	92	69.1	1.33	168	158.3	1.06
Other non-rural places	341	315.3	1.08	584	607	0.96
Nonmetropolitan rural areas	143	146.1	0.98	182	214.4	0.85
	Chi sq. = 9.75, p<0.01			Chi sq. = 6.4, p<0.05		

SOURCE: Goldsmith (1980), Table 7; Hammond (1972)

*The observed and expected number of lung cancer deaths listed by place of residence and by occupational exposure (to dust, fumes, gases, or X-rays), and adjusted for age and smoking habits, is confined to men who had lived in the same neighborhoods for more than 10 years. The subjects were among a population of 1,064,004 men and women studied by the American Cancer Society (Hammond 1972).

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TABLE E-2

RELATIVE RISKS IN MEN OF LUNG CANCER MORTALITY (ADJUSTED FOR AGE AND SMOKING) BY RESIDENCE AND OCCUPATIONAL CATEGORY

Derived by Comparing Residents of Metropolitan Counties
and Urban Sections of Nonmetropolitan Counties with Residents
of Rural Sections of Nonmetropolitan Counties (25-State Study,
Confined to Men Residing in Same Neighborhood for Last 10 Years)

	Occupationally Exposed*	Not Occupationally Exposed*
Metropolitan Counties		
Greater than 1 million residents	1.26	1.16
Less than 1 million residents	1.17	1.14
Nonmetropolitan Counties		
Urban	0.99	1.18
Rural	1.00	1.00
Weighted Relative Risk, Urban** (U.S. population 1970)	1.19	1.16
Overall Weighted Relative Risk***	1.17	

SOURCE: Adapted from Hammond and Garfinkel (1980), Table 1, p. 208

*To dust, fumes, gases, or X-rays

**Relative risk of lung cancer mortality in metropolitan counties and urban sections of nonmetropolitan counties (weighted according to population data from U.S Bureau of the Census 1980)

***Weighted by the proportion of men in occupationally-exposed and nonexposed categories in study population of Hammond and Garfinkel (1980)

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TABLE E-3

ATTRIBUTABLE RISKS OF LUNG CANCER MORTALITY (ADJUSTED FOR AGE AND SMOKING) U.S. MALES (25-STATE STUDY) DUE TO URBAN FACTOR AS AN INDICATOR OF AIR POLLUTION

COMPARISON

Residents of Metropolitan Counties and Urban Sections of Nonmetropolitan Counties with Residents of Rural Sections of Nonmetropolitan Counties; Proportion (p) "exposed" in U.S. Population in 1970 is 0.816 (U.S. Bureau of the Census 1980)

	Relative Risks (RR)	Attributable Risks (AR)
Occupationally Exposed*	1.19	13.4%
Not Occupationally Exposed*	1.16	11.6%
Overall**	1.17	12.2%

*to dust, fumes, gases, or X-rays

**weighted according to the proportions of occupationally exposed and nonexposed men in the study population of Hammond and Garfinkel (1980)

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deaths per 10^5 exposed urban men. To convert this rate to a rate for the general urban population, we multiply by 0.82 (see Appendix D) and obtain 6.7 deaths/10^5 urban persons. The proportion of the population that is urban according to the categories established originally by Hammond and Garfinkel (1980) is the proportion living in metropolitan areas plus those living in urban sections of nonmetropolitan areas, that is, all persons not living in the rural areas of nonmetropolitan areas. In 1970, this proportion was 81.6% (U.S. Census Bureau 1980), leading to an estimate of 5.5 deaths/10^5 persons/year in the U.S. population (6.7 x 0.816). Note that we use the same proportion for occupationally exposed and unexposed, although it is more likely that a higher proportion of occupationally exposed persons are also urban residents.

This estimate of attributable risk has several limitations. First, the method of standardization for smoking habits was not described, so it is possible (as suggested by several commenters) that the correction was incomplete and that some fraction of the unexplained urban effect was due to differences in some aspects of smoking habits (such as age at starting to smoke), for which standardization was not carried out. However, the ACS study collected information on a variety of aspects of smoking habits and revealed no effect of age at starting to smoke. Moreover, as discussed in the text, the data of Haenszel et al. (1956) revealed no systematic differences in age at starting to smoke in any age-group studied in 1955.

Second, the aggregation of the data into three broad residence categories by Goldsmith (1980) and subsequently into two categories in Table E-2 may have obscured some differences. Although Hammond and Garfinkel (1980) presented data for more residence categories, these were aggregated by Goldsmith, and it was not possible to use the disaggregated data because Hammond and Garfinkel's residence categories cannot be matched to data from the U.S. Census. In the absence of specific reasons to suspect bias, aggregation of data is generally expected to result in the reduction or masking of associations by pooling individuals with greater and lesser exposure within each category.

Third, the study population in the ACS survey, although it contained many residents of large urban areas, is not likely to have been representative of the entire U.S. population (cf. Sterling 1975). It had a different age distribution and included more white-collar workers, higher educational levels, and a higher socioeconomic class on the average than did the general U.S. population. Thus, the proportion of occupationally exposed, which was classified on the basis of self-reported exposure to "dust, fumes, vapors, gases, or X-rays" (Hammond and Garfinkel 1980, p. 4) may be underestimated, and the proportion living in urban areas with the highest air pollution levels (i.e., residents of inner cities) may also be underestimated.

Several attempts have been made to estimate the possible magnitude and consequences of this selection bias. Karch and

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Schneiderman (1981) suggested that the attributable risk from urban residence (unexplained urban effect) might have been underestimated by a factor of about 2.1: this estimate was based on a comparison of the data of Hammond and Garfinkel (1980) with those of Haenszel and Taueber (1962). Doll and Peto (1981) suggested that the selection bias in the ACS study had led to underestimation of the effects of alcohol by a factor of about 2 (footnote c to Table 11), and to underestimation of the effects of occupation by a factor of about 3.3 (p. 1244). CAG (1982) matched data on social stratification of the ACS population to data on the relationship between exposure to BaP and socioeconomic stratification, and suggested that the ACS population would have been exposed to average levels of BaP only 70% of the U.S. average. Although all these estimates are somewhat speculative, the consensus view is that selection bias in the ACS study is likely to have reduced the apparent magnitude of these risk factors by factors between 1.44 and 3.3.

Strictly, our estimates of attributable risk in Table E-3 are estimates of the "unexplained urban effect "--i.e., the fraction of the excess urban lung cancer rate that is not explained by standardization for recorded differences in smoking and occupation. In principle, this "unexplained urban effect" might include contributions from other factors (such as unrecorded aspects of smoking behavior) as well as from air pollution. However, in the remainder of this Appendix we will use our estimates as a measure of the effects of air pollution. In

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the absence of reliable data on air pollution levels at the appropriate period in the 1930s and 1940s, we will relate the excess cancer mortality in the 1960s to the level of 3.5 ng/m^3 BaP characteristic of U.S. population exposure in the early 1960s (see CEQ 1980, and discussion in the text). (This procedure, although questionable, is similar to that used for other estimates tabulated in Table IV-1, and its consequences are discussed in the text.). Using CAG's (1982) estimate that the ACS population was exposed to an average level of BaP only 0.70 times the U.S. average, we estimate the average exposure of the ACS population to be about 2.5 ng/m^3 BaP.

Related to an average exposure to air pollution characterized by 2.5 mg/m^3 BaP, an estimate of 5.5 deaths/10^5 persons/year corresponds to a dose-response coefficient of 2.2 deaths/10^5 persons per ng/m^3 BaP. This is the figure included in Table IV-1.

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APPENDIX F

TIME TRENDS IN LUNG CANCER RATES

In principle, changes in mortality and incidence rates with time can provide clues as to the causes of disease. Changes in exposure to a causative agent should, after appropriate latent periods, be followed by changes in incidence and mortality of the disease in the exposed cohorts. Thus trends in age- and sex-specific incidence and mortality rates can provide supporting evidence for the existence of an association that is hypothesized for other reasons. Likewise, observed trends that are not consistent with an hypothesized association may provide substantial evidence against the hypothesis--or at least indicate that another causative factor is involved.

To test the hypothesis that air pollution plays a role in the etiology of cancer, it would be desirable to compare age- and sex-specific trends in cancer rates to earlier trends in exposure to air pollution. However, as explained in Section II.D.2.d of this report, there is insufficient evidence in trends in exposure to make specific predictions, since downward trends in the ambient concentrations of some air pollutants have been offset by upward trends in others. However, data on trends in cancer rates are of some importance in considering one specific issue. Doll and Peto (1981) presented arguments that available data on trends in lung cancer rates could be adequately explained by the available information on changes

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in smoking habits, without the necessity for invoking other causative factors. This conflicts with an earlier conclusion by Schneiderman (1978). In this appendix we review data bearing on this dispute, including more recent analytical studies by Manton (1982) and Janis (1982). This review is necessarily limited to lung cancer, because there are insufficient data on the contribution of smoking to cancers at other sites.

Examination of the data on cancer deaths in the United States for the last 30 years reveals a steady increase in the overall age-adjusted mortality rate (USDHEW 1980). Incidence rates have also increased, although not as consistently. Between the First National Cancer Survey in 1937-39 and the Second National Cancer Survey in 1947-48 (Dorn and Cutler 1959), the overall age-adjusted incidence rate for cancers at all sites rose by approximately 11%. Subsequently, between the Second National Cancer Survey and the Third National Cancer Survey in 1969-71 (Cutler and Young 1975), the age-adjusted incidence rate declined by 4%. In analyzing data from the Third National Cancer Survey and the NCI Surveillance, Epidemiology, and End Results (SEER) program (Young et al. 1978), Pollack and Horm (1980) concluded that, between 1970 (average of 1969-71) and 1976, the overall age-adjusted cancer incidence rate was again rising. They found an increase of approximately 10% during that 5-year period. Because age-specific trends in cancer are not constant across all ages (i.e., decline in youngest age groups and increase in older groups), it is important to examine age-specific rates separately.

There is evidence that the Third National Cancer Survey produced inconsistent estimates for the 3 years 1969-1971; 1969 appears to have included some prevalence cases, i.e., cases diagnosed earlier than 1969, and 1971 (the last year of the survey) may have been under-reported. Pollack (1980) has since reported incidence data derived completely from the SEER program for 1973-1977, which should be free of these possible flaws. The SEER data show increases in total (age-adjusted) cancer incidence of 6.8% in white males, 3.8% in white females, 3.4% in black males, and 2.4% in black females during the 4-year period.

A major portion of the increase in cancer mortality and incidence rates is due to an increase in lung cancer. This increase in lung cancer is a general phenomenon in industrial countries. Increases in cancer of the respiratory tract are appropriately attributed largely to cigarette smoking, and secondarily to occupational exposure, environmental pollution, or other sources.

In England and Wales, for example, there was a 10-fold increase in death rates from lung cancer from 1901 to 1930 and an additional 10-fold increase from 1930 to 1960 (Katz 1964). In Canada, the male death rate from lung cancer increased from 3.0 per 100,000 in 1930 to 24.6 per 100,000 in the 1960 population (Katz 1964). In Switzerland, a 32-fold increase occurred between 1900 and 1952 (Cleary 1963). From 1933 to 1960, the annual lung cancer death rate in Australia increased from 3.15 per 100,000 to 28.9 per 100,000 for males and from 2.02 per 100,000 to 4.2 per 100,000 for females (Cleary 1963).

In the United States, the lung cancer mortality rate for males has increased more than 25-fold in 45 years and is now increasing even more rapidly for women (NCHS 1980). During the period between the Second National Cancer Survey and the Third National Cancer Survey (1947-1970), the incidence of lung cancer more than doubled in men and women, and in blacks and whites (Dorn and Cutler 1959, Cutler and Young 1975). Rates for black males have increased more rapidly than for white males. Projections for 1981 are 122,000 new cases of lung cancer and 105,000 deaths (ACS 1980).

A comprehensive study of lung cancer in Western Europe was made in 1969 by the World Health Organization (WHO) Working Party on Cancer Statistics. The study revealed that over the previous 10 years, lung cancer mortality had increased by 8% for males and 3.1% for females. The conclusion was that the observed increase in lung cancer death rates was real and not an artifact of better diagnosis or reporting or of longer life span.

In West Germany, lung cancer deaths increased from 6,296 in 1952 to 15,000 in 1965. According to Wagner (1971) during this period there was no significant change in efficiency of diagnosis or reporting. To determine whether increases in

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lung cancer (in Denmark) were real or due to more accurate diagnosis, X-rays taken during the course of examinations for detection of pulmonary tuberculosis were reexamined. The X-rays did not reveal many misdiagnosed cancers, and it was concluded that a true increase in lung cancer incidence had occurred (WHO 1969).

There is considerable disagreement over the full set of reasons for these increasing rates. Both direct industrial exposure and air pollution levels have been suggested as contributing to the increases--as well as cigarette smoking (Davis and Magee 1981). Doll and Peto (1981) compared age-specific lung cancer mortality in England and Wales with lung cancer mortality in the United States, relating each to cigarette smoking (their tables E5 and text Figure E4, summarized here in Table F-1). From about 1900 to 1920, British cigarette sales were higher (per capita older than 15) than U.S. sales (per capita older than 18). From 1920 to 1940, U.S. and British sales were almost equivalent; from roughly 1942 on, U.S. sales have been substantially higher than in Great Britain. In the youngest age groups (30-34 and 35-39), mortality per million men in 1978 was almost identical in the two countries. This appears to be inconsistent with the substantially greater number of cigarettes consumed after 1940 by U.S. men if cigarette smoking were the sole cause. For the age groups 40-44 and 45-49, U.S. mortality in 1978 was 25-40% higher than in Great Britain. For men older than 55, the mortality rates in Great

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TABLE F-1

CIGARETTE SMOKING PER ADULT* AND LUNG CANCER MORTALITY IN MALES, ENGLAND AND WALES, UNITED STATES

			England and Wales		United States	
Age in Years (1978)	Approximate Year of Birth	Approximate Year Started Smoking**	Approximate Number of Cigarettes Sold Per Adult*	Lung Cancer Mortality Per Million	Approximate Number of Cigarettes Sold Per Adult	Lung Cancer Mortality Per Million
30-34	1946	1966	7.5	17	11.5	17
35-39	1941	1961	7.5	63	11.9	62
40-44	1936	1956	6.5	138	10.0	192
45-49	1931	1951	6.1	385	10.6	480
50-54	1926	1946	7.0	1,047	9.7	1,021
55-59	1921	1941	6.0	1,912	6.0	1,647
60-64	1916	1936	4.3	3,315	4.3	2,625
65-69	1911	1931	3.8	5,018	3.8	3,557

*In Great Britain--persons over 15
In United States--persons over 18

**Assuming age 20 as starting age

SOURCE: Doll and Peto (1981), Table E4 and Figure E5

Britain in 1978 were substantially higher, despite the fact that average numbers of cigarettes smoked were roughly equal at the time these men started smoking. The Doll and Peto tabulation ends at age 69. In the United States, the greatest increases in lung cancer mortality between 1968 and 1978 were in men aged 75-84 (Davis et al. 1982).

Two possible explanations for these inconsistent results suggest themselves: (1) other characteristics of smoking, such as the age at starting, are (or were) substantially lower in Great Britain than in the United States, and/or (2) other things in the environment (e.g., industrial exposure, air pollution) led to higher rates in Great Britain despite lower smoking levels than in the United States.

There is at least one other way of looking at the time-trend (cohort) data. The U.S. Surgeon General, in his report entitled Health Consequences of Smoking (1982, pp. 51, 53, and p. 56-57), has reported smoking data by year of birth (in 10-year intervals--e.g., 1901-1910) and cancer mortality for age-specific groups (e.g., 30-34, 35-39, etc.). From these data it is possible to find birth cohorts with similar cigarette-smoking patterns and then to compare their lung cancer mortalities at specific ages. (See Figures F-1, F-2, and F-3, derived from Figures 12, 14, and 16 of that report.) For example, for men born between 1901 and 1910, 62% was the maximum that ever smoked. The next cohort with a similar maximum was the group born between 1931 and 1940. The median age of starting

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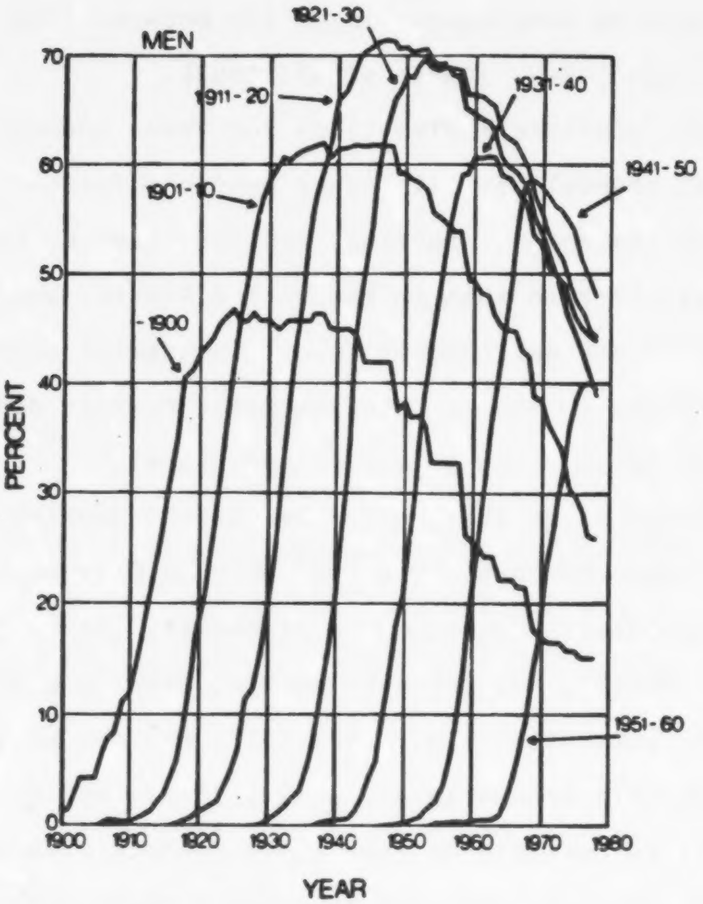
FIGURE F-1

CHANGES IN THE PREVALENCE OF CIGARETTE SMOKING AMONG SUCCESSIVE BIRTH COHORTS OF MEN, 1900-1978



Note: Calculated from the results of over 13,000 interviews conducted during the last two quarters of 1978, provided by the Division of Health Interview Statistics, U.S. National Center for Health Statistics

SOURCE: USDHHS 1982

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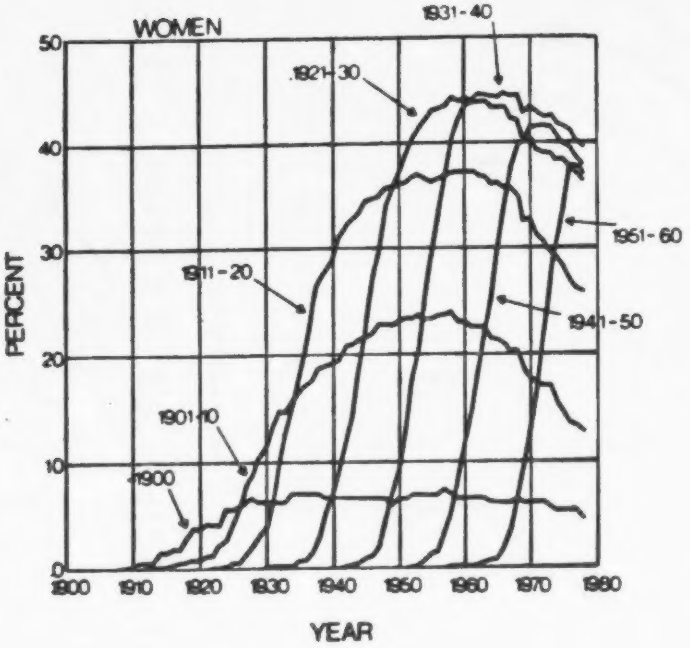
FIGURE F-2

CHANGES IN THE PREVALENCE OF CIGARETTE SMOKING AMONG SUCCESSIVE BIRTH COHORTS OF WOMEN, 1900-1978



Note: Calculated from the results of over 13,000 interviews conducted during the last two quarters of 1978, provided by the Division of Health Interview Statistics, U.S. National Center for Health Statistics

SOURCE: USDHHS 1982

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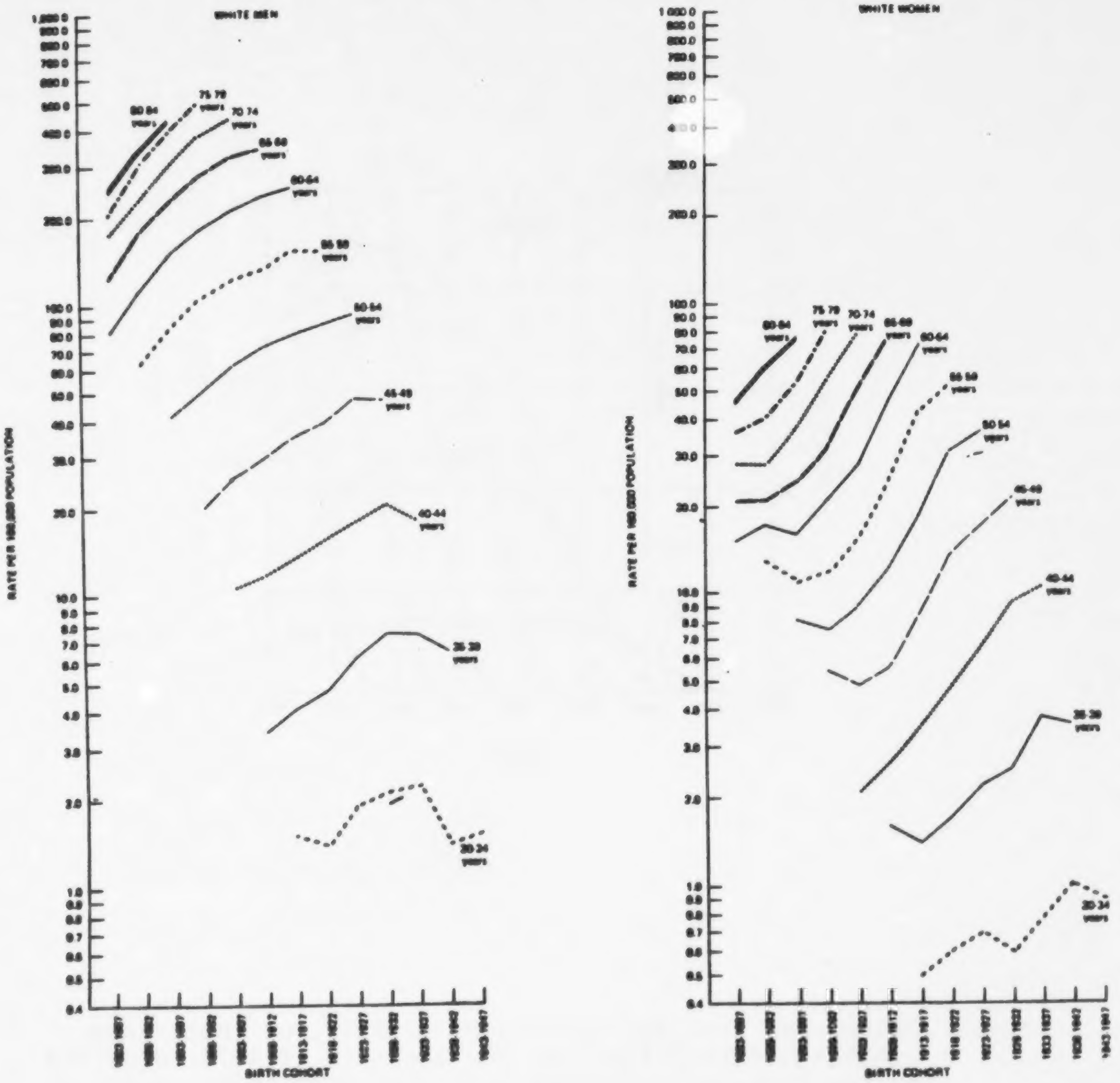
FIGURE F-3

MORTALITY RATES FOR MALIGNANT NEOPLASMS OF THE TRACHEA, BRONCHUS, AND LUNG, FOR WHITE MEN AND WHITE WOMEN, BY BIRTH COHORT AND AGE AT DEATH, UNITED STATES, 5-YEAR INTERVALS DURING 1947-1977



Note: Calculated from the results of over 13,000 interviews conducted during the last two quarters of 1978, provided by the Division of Health Interview Statistics, U.S. National Center for Health Statistics

SOURCE: USDHHS 1982

to smoke was about 17 for the 1901-1910 men, and about 16 for the 1931-1940 cohort. The lung cancer mortality rates for men aged 40-44 years born in 1931-1940 were almost double the rates for men born 1901-1910, whose smoking patterns were similar. For women the comparable smoking cohorts are 1921-1930 and 1931-1940, separated by only 10 years. The second (more recent) cohort of women has a 25-60% higher lung cancer mortality rate at comparable ages (30-44); a 25% increase in 10 years is equivalent to a doubling in 30 years: $(1.25)^3 = 1.95$.

Table F-2 gives the smoking data for men. Similar data for women can be derived from the Figures F-1, F-2, and F-3 from the Surgeon General's report.

TABLE F-2

SMOKING HISTORY: U.S. MALES

Decade of Birth (mid-year) (1)	Maximum Percent Smoking (2)	Year of Maximum (3)	Year of 50% of Maximum* (4)	Median Age Beginning to Smoke (4)-(1) (5)
1891-1900 (1895)	47	1924	1913	18
1901-1910 (1905)	62	1938	1922	17
1911-1920 (1915)	72	1946	1933	18
1921-1930 (1925)	70	1952	1942	17
1931-1940 (1935)	61	1962	1951	16
1941-1950 (1945)	58	1968	1961	16
1951-1960 (1955)	Possibly not yet reached			Inappropriate

*Year of median starting to smoke

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Calculations attributing increases in lung cancer to a single cause, such as smoking, ignore the multicausal nature of carcinogenesis and possible interactions with air pollution or other factors. Although there is little doubt that cigarette smoking has played a major causative role in the increase in lung cancer, not all lung cancer, even among those who smoke, can be attributed solely to cigarettes.

The discrepancy noted between the trends in lung cancer mortality rates for U.S males (rate of increase now decreasing) and U.S. females (rate of increase now increasing) has been suggested as being incompatible with the argument that air pollution has a major influence on lung cancer rates. These trends are said to be more consistent with changes in cigarette consumption (with a 20-year lag period) (Doll and Peto 1981). However, rates in black women, who smoke less and who in general started smoking at a later age, are almost identical with rates in white women--and have increased equally rapidly.

Schneiderman (1978) attempted to account for the effects of smoking on trends in cancer rates by estimating the proportion of lung cancer, as well as several other types of cancer, that could be attributed to cigarette smoking at different time periods. When this proportion was subtracted from the total, he found that there had been a substantial increase in the residual lung cancer rate, i.e., the fraction of lung cancers attributable to factors other than smoking, between 1947 and 1969-1971. More recently, Schneiderman (1979), using the data of Pollack and Horm (1980), to calculate the increases between the Third National Cancer Survey and the 1976 SEER survey in lung cancers not related to smoking, found that the fraction of lung cancers not attributable to smoking had risen substantially during that period. Schneiderman's methodology is, however, deficient in at least two respects: (1) he attributed all "interaction-with-smoking" cancers to smoking alone, and (2) he neglected cohort effects.

Several more sophisticated attempts have been made to take cohort effects into account in looking at the time trends in lung cancer. In one of these, Manton et al. (1982) commented on their own findings and those of two other published studies:

> These results suggest that, at most, we can attribute between 79 and 92 percent of the increase (from 1950 to 1977) in U.S. white male lung cancer mortality to corresponding increases in cigarette consumption. For U.S. white females the pattern is less obvious with between 62 and 100 percent of the increase in lung cancer as the maximum attributable to smoking.

Manton cited two cohort studies of British data (Townsend 1978, Stevens 1979) that showed attributable risks for males at 94% and 89%, and for females at 71% and 94%, respectively. It was not clear if these attributions were percentages of total lung cancers, or percentages of changes.

Two additional cohort studies have been recently published (Osmond 1982, Janis 1982). The study by Osmond discussed lung cancer in women (and bladder cancer in men) and noted

> ...that women started smoking later than men is reflected in the later position of the peak cohort for lung cancer, 1925/6 rather than 1900/1. Numbers of cigarettes smoked by successive generations of

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> either sex (in the U.K.) have not declined to any great extent, raising the question as to what has caused lung cancer decreases (in younger persons). Reduction of tar content of cigarettes has been suggested (Doll and Peto 1981), but not unanimously accepted (Gerstein and Levison 1982). Alternatively, reductions of air pollution may have been important.

Janis noted that the peak cohort for British and U.S. (white) males was the same (1900); this implies temporal similarities in cigarette-smoking patterns in the two countries, which in turn raises questions as to why age-standardized rates of lung cancer have begun to fall in Great Britain, but not in the United States. These several studies raise doubts about the cohort effect (reflecting between-cohort differences in cigarette smoking patterns) as the sole reason for the continuing increase in lung cancer mortality in the United States.

The Manton data, however, indicated a possible U.S. peak cohort born later than 1891-1900, although at the time of the Manton review the peak rate had occurred in white men born about 1900. In contrast to Janis, Manton found that the highest "susceptibilities" were in the youngest cohort, but that the rates for these men, in turn, were likely to be modified (downward) by decreasing proportions of regular smokers and by changed (lower tar) cigarettes. No studies of cohort effects in black males, who currently have a 40% higher lung cancer mortality rate than white males despite lower (tar-weighted) cigarette consumption, have come to our attention.

Janis (1982) reported an independent "year" effect (i.e., a temporal effect not associated with a specific cohort effect)

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with increasing risk year-by-year. Manton's model has an operational counterpart in a measure of "susceptibility." For each succeeding cohort Manton found increasing "susceptibility" over time in both men and women. A possible explanation of the findings of both Janis and Manton is an interaction among environmental or industrial pollutants that may have increased over time, giving an appearance of a "year" effect (or increased susceptibilities of cohorts). Janis also noted that British lung cancer rates rose more rapidly than U.S. rates, and have now begun to fall more rapidly. This, too, suggests an interaction with general air pollution (higher in Great Britain), which has sharply abated in Britain (since the 1950s-1960s). As noted earlier, U.S. lung cancer rates have not been as high as British rates, particularly at older ages. Consistent with the cigarette smoking explanation is the rapid decline in lung cancer mortality (relative to continuing smokers) after cessation of smoking. That conditions in Britain are not strictly comparable to those in the United States is suggested by the fact that, among British physicians who have stopped smoking, lung cancer mortality rates appear to level off (after 15 or more years cessation) to about twice those of nonsmokers (Doll and Peto 1977), whereas in the United States it has been reported that the rates of stopped smokers, after 15 years of not smoking, reach those of men who never smoked (Wynder et al. 1970).

A recent report of the National Academy of Sciences/National Research Council (Gerstein and Levison 1982) raised substantial

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doubts about the positive health effects of reduced tar/nicotine cigarettes. The report concluded

> ...while some large scale studies have suggested small gains in health due to using lower T/N (or filter rather than non-filter) cigarettes, other population-wide studies do not support this view. Thus, the evidence for switching to lower T/N cigarettes is doubtful." (Emphasis original)

Calculations based on the National Cancer Institute data for 1973-1977 (SEER), which did not include cohort effects, suggested that less than 20% of the increased incidence in cancer in white males, and less than half the increased incidence in white females, were attributable to cigarette smoking (Schneiderman 1978). These estimates did not take into account interactions or the reduced proportion of all adults smoking cigarettes and the reduced tobacco and tar content of the cigarettes sold since 1965 (USDHEW 1979).

The increase in lung cancer incidence and mortality during the 1970s is of particular interest. Such a change is consistent with an increase in exposure to some environmental factor or factors other than smoking during the 1940s or early 1950s. As noted by Rall (1978), Epstein (1978), and Davis and Magee (1979), this is the period of the initial rapid growth in the synthetic organic chemical production, as well as a period of increased activity in other industries, including the use of asbestos.

Evidence that there have been increases in lung cancer independent of smoking habits was given by Enstrom (1979), who studied lung cancer mortality rates for nonsmokers in the

United States. He found that these rates had risen considerably between 1914 and 1968 and appear to have doubled during the period between 1958 and 1968. This finding was questioned by Doll and Peto (1981) on the grounds that Enstrom may have included ex-smokers in his nonsmoker category. Enstrom's finding is in contrast that of Garfinkel (1981b) who reported no such increase in the population followed by the American Cancer Society.

Garfinkel also cited a similar result from the nonsmokers in the Dorn study of veterans (Rogot 1980). On closer examination, however, both these sets of data exhibit peculiarities (or fluctuations), due to small numbers or possibly to reporting errors. Following specific birth cohorts, three of Garfinkel's groups of male nonsmokers (persons born about 1916, 1901, and 1886) showed declines in age-specific rates in the third time period--to levels in the 1916 and 1901 cohorts below those shown by any of the other cohorts at the same attained age. (The 1886 cohort could not be used in this comparison because other cohorts had not attained ages 85-89.) This is contrary to the general pattern of increase in cancer mortality rates with increasing age (except for the very oldest persons). Excluding these aberrant points, which suggest that recent follow-up may have been incomplete, each succeeding cohort of males shows a higher lung cancer rate (at the same attained age) than the preceding cohorts--with only one exception: men born about 1896 had lower rates at ages 70-74 than did

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men born about 1891 (26.4 vs. 32.3). The data for the women in the ACS study show similar patterns (with the 1916 cohort also showing an unexpected inversion in the last follow-up period). The rates for women nonsmokers, which are based on larger numbers, are otherwise more consistent than those for men. The Dorn data are also erratic. The 1901 cohort has lower lung cancer rates reported for ages 60-64 than for ages 55-59. Except for this and one other data point (men born about 1896, attained age 65-69), the men reported in the Dorn data show somewhat higher rates for the same birth cohorts and for the same attained ages than the ACS study. This is in keeping with the nature of the ACS sample--somewhat less urban, somewhat less "blue-collar", somewhat higher education and social class than the United States as a whole. The Dorn population, while derived only from men healthy enough to have been in the military, is likely to be closer to the general U.S. population.

It is worth noting that Dean et al. (1978) also reported substantial increases in rates among nonsmokers. In contrast, Doll (in Magnus 1982) apparently assumed no change over time in lung cancer mortality among nonsmokers in the United States from 1933 to 1977. This is rather surprising because in his Figure 1 (page 224) in which he plotted rates for nonsmokers (age-adjusted) for 1960-1972 (from Hammond), the nonsmoker rates for several of the early years are higher than the rates for the total populations, also age-standardized--considered separately by sex.

Attempts have been made to study the trends in cancer mortality rates following apparent reductions in pollution. Higgins (1974) was able to account for increases in lung cancer in the United States and England up to about 1970 by changes in smoking habits. He found more recent rates inconsistent with cigarette smoking. He attributed the decline in lung cancer rates in England, which began as early as 1960, to the dramatic reduction in air pollution. This relationship is supported by the finding that the earliest (and greatest) reduction in lung cancer rates occurred in London where there was also the earliest and greatest reduction in measured air pollution. A similar conclusion appears to have been reached by Lawther and Waller (1978), who found that the lung cancer trends from 1951 to 1973 in Greater London and the rural districts of England and Wales were moving in opposite directions. The rates declined in London, where the Clean Air Acts had been first put into effect, while they were increasing in the rural areas. Todd et al. (1976), in analyzing cancer mortality rates and cigarette consumption in England, found additional evidence supporting the hypothesis that atmospheric pollution interacted with cigarette smoking to increase the incidence of lung cancer. They argued that the finding that the male cohorts with the highest "cumulative consumption of constant tar cigarettes" were 5 or 10 years younger than those that experienced the

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highest age-specific lung cancer mortality rates (at all ages between 30 and 59 years) implied the existence of etiological agents (in addition to cigarette smoking) that influence the development of lung cancer in humans.

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APPENDIX G

CRITIQUE OF TWO RECENT REVIEWS

This Appendix discusses two recent reviews which have concluded that the contribution of air pollution to cancer risks is small and/or indeterminable. Doll and Peto (1981) presented a comprehensive review of data on cancer rates in the U.S. population and their known or presumed association with various environmental factors. Their final conclusion (Table 20) was that about 2% of all cancer deaths in the U.S. (possible range, less than 1% to 5%) could be attributed to pollution of all kinds. This estimate appears to include about 1% attributed to the effect of urban air pollution on lung cancer (p. 1248). Although this estimate is consistent with others reviewed in this report (see Table IV-1), Doll and Peto expressed considerable reservation about the reliability of these estimates and the methods used to derive them.

The precise basis of Doll and Peto's conclusions is difficult to determine from their paper. In their section on air pollution (pp. 1246-1248) they cited no specific epidemiological studies of the association between cancer rates and any specific pollutants, and only two studies of urban/rural differentials. One of these was their own unpublished study of British doctors, presented in a footnote (see Section II.B of this report for discussion). The other was the paper by Hammond and Garfinkel (1980): they cited this paper as demonstrating an urban/rural

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differential after standardizing for age and six categories of current smoking. They then added:

> These differences do not allow for differences attributable to occupational hazards but even so are not large, and much or all of them might be due to the expected effects of early cigarette usage. The authors allowed for occupation by examining separately men exposed and not exposed to dust, fumes, etc. and concluded that their data offer "little or no support to the hypothesis that urban air pollution has an important effect on lung cancer."

It is evident from these statements that Doll and Peto had not conducted an independent analysis of these data (cf. Appendix E).

Doll and Peto expressed considerable skepticism about the possibility of detecting effects of urban air pollution (or other regional effects):

> Some investigators have attempted to estimate the effect of pollutants by comparing the lung cancer mortality rates in different areas and "making allowance" for differences in smoking habits by retrospective inquiry of the amount smoked by representative residents. We doubt, however, whether it is possible in this way to disentangle the effects of smoking and environmental pollution, especially in those studies that have examined cancer rates only within categories of men with such broadly similar smoking habits as nonsmokers (including ex-smokers), current smokers smoking 20 cigarettes a day or less, and current smokers smoking more. Such broad classes are hardly likely to take account of differences in a habit which may affect the incidence of lung cancer by up to fortyfold sufficiently accurately for a twofold urban-rural difference to be estimated with certainty.

They continued by pointing out the difficulty of controlling for other aspects of smoking, including age at starting, type of cigarette, depth of inhalation, etc. (see Chapter II). However, their discussion of urban/rural differences in these aspects of smoking was speculative, and they did not cite any specific data (such as those of Haenszel et al. included in this report as Table II-4) on urban/rural differentials in these aspects of smoking. They did not cite the study of Dean et al. (1977, 1978) in which these factors were measured, reported, and controlled for.

Much of Doll and Peto's skepticism about the role of air pollution appears to stem from their conclusion that cigarette smoking can account for most, if not all, of the geographical and temporal patterns in lung cancer rates. (They did not discuss effects of air pollution at sites other than the lung.) They estimated that as much as 91% of lung cancer in males and 78% of lung cancer in females was attributable to cigarette smoking. These figures are higher than most other estimates, and the method used for arriving at them is subject to upward bias. Specifically, Doll and Peto used the data from the ACS survey (Garfinkel 1980) to estimate lung cancer rates in nonsmokers, used these rates to estimate the number of lung cancers that would have occurred in the United States without smoking, and attributed all the rest to smoking. However, as pointed out earlier, the ACS survey was a biased sample of the U.S. population. Doll and Peto recognized this bias in their calculation of risks due to alcohol (Table 11) and occupation (p. 1244), for which they estimated that the ACS sample underestimated national risks by factors of 2.0 and 3.3, respectively. However, they did not take any account of this bias in their estimate of smoking risks. Also, Doll and Peto's procedure would include all interactions in the category of cancers attributed to smoking.

Doll and Peto's actual numerical estimate of the fraction of cancers attributable to air pollution appears to be derived from the study of Pike et al. (1975) and the more informal review by Cederlof et al. (1978), both of which led to

> the conclusion that atmospheric pollution, in conjunction with cigarette smoke, might have contributed to some 10% of all cases of lung cancer in big cities (and so to a few percent of lung cancer in the country as a whole, i.e., about 1% of all cancer).... These crude estimates provide the best basis for the formation of policy.

Doll and Peto did not review the other studies listed in Table IV-1 in this report, and did not consider the point made in Chapter IV, that extrapolation from data on persons exposed to high concentrations of products of incomplete combustion, using BaP as an index, yields estimates only of the fraction of lung cancers associated with these components of air pollution, and not with other components.

In summary, Doll and Peto's conclusions about air pollution were informal and do not appear to be based on a critical review of the limited literature which they cited.

Shy and Struba (1982) presented another review of scientific evidence on the association between air pollution and cancer. They recognized the existence of four of the "converging lines of evidence" that have been reviewed in this report: the unexplained urban factor, the known carcinogenic effects of combustion products in workers occupationally exposed to high concentrations, the geographic correlations between lung cancer rates and some indices of air pollution, and the presence of carcinogenic substances in ambient air. However, they concluded:

> In spite of these converging lines of evidence, we will argue in this section that firm conclusions about air pollution and lung cancer are simply not warranted by the current state of knowledge. Serious deficiencies exist in making even qualitative estimates of persons exposed or not exposed to atmospheric carcinogens. Analytic (individual risk) studies of air pollution as a human carcinogen have not yet been reported, and none of the epidemiologic studies allows one to make a direct link between lung cancer incidence and exposure to air pollution. The supporting arguments for this judgment will be given as we review the epidemiologic evidence in the following parts of this section.

Although Shy and Struba cited more studies of the association between air pollution and cancer rates than Doll and Peto, they nevertheless listed only a limited number of papers, and did not cite the studies that we regard as individually most persuasive (e.g., Dean et al. 1978, Hammond and Garfinkel 1980). They dismissed studies of urban/rural differentials with the following incorrect statement:

> Thus far, none of the studies provide even qualitative estimates of personal exposure to ambient air pollution, and all lack any quantitative data whatsoever on carcinogenic levels in the ambient air.

As noted in the test, they dismissed as "extremely low" a calculated risk from ambient concentrations of BaP that actually falls within the range of other estimates (see Table IV-1).

Although Shy and Struba's critical approach to the studies they cited is appropriate, their standards of proof seem unreasonably high:

> It would seem essential, in future epidemiologic studies, to identify cohorts exposed to specific classes of suspected atmospheric carcinogens, such as formaldehyde in particle board, plastic vapors, indoor cigarette smoke, classes of solvents in closed environments, motor vehicle diesel exhaust, and so on. Many of these exposure situations may be best studied in an occupational setting, but the characterization of chemical species and dose will be difficult in any environment. General population-based studies do not promise satisfactory results, owing to the heterogeneity of exposure and lack of individual data on confounding factors in most such studies.
>
> ...The proposed approach for advancing our knowledge in this area is to define individual exposure to specific sources of atmospheric carcinogens, to attempt to characterize this exposure in terms of specific organic chemical classes of compounds, and to use these exposure characterizations as a basis for well-designed analytic epidemiologic studies. It is hoped that this approach will yield more testable and refutable hypotheses than have been developed to date.

Their insistence on rigorous, analytic (apparently prospective and long-term) studies reflects a reluctance to consider the weight of evidence provided by the large body of literature on this subject, much of which they did not cite.

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APPENDIX H

DATA ON SMOKING HABITS IN NORTHEASTERN ENGLAND

Tables H-1 to H-4 summarize data on three characteristics of smoking habits (age at starting to smoke, depth of inhalation, and proportion of filter cigarettes), stratified by age, sex, and location of residence. These data were derived from a survey in northeastern England and were originally published as Tables H17, H18, H21, and H24 in Dean et al. (1978).

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TABLE H-1

DISTRIBUTION OF AGE AT STARTING TO SMOKE BY AREA AND SEX IN THE LIVING POPULATION, 1973

	Eston		Stockton		Rural Districts	
	Male (%)	Female (%)	Male (%)	Female (%)	Male (%)	Female (%)
Number 35+	7,230	7,570	18,370	20,460	15,380	16,510
Age at starting to smoke						
<15	18.3	7.6	14.5	4.7	11.7	2.2
15-19	43.0	21.6	41.5	23.1	36.3	17.8
20-24	12.6	10.5	11.5	8.9	10.3	8.3
25+	5.9	10.3	8.2	13.2	5.7	8.7
Smokers, unclassified	2.1	1.4	5.4	1.9	6.9	1.7
Never smokers	18.1	48.5	19.0	48.2	29.1	61.4

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TABLE H-2

DISTRIBUTION OF AGE AT STARTING TO SMOKE BY AREA AND SEX IN THE LIVING POPULATION, 1973

	Eston		Stockton		Rural Districts	
	Male (%)	Female (%)	Male (%)	Female (%)	Male (%)	Female (%)
Number 35-44	2,270	1,980	4,950	5,220	4,750	4,460
Age at starting to smoke						
<15	15.5	11.7	9.4	8.1	8.6	1.2
15-19	45.0	37.9	47.2	30.4	39.5	27.2
20-24	14.0	15.2	11.0	8.9	11.1	10.1
25+	1.6	4.1	4.7	12.6	5.6	8.9
Smokers, unclassified	1.6	0.7	8.7	1.5	4.3	1.2
Never smokers	22.5	30.3	18.9	38.5	30.9	51.5
Number 45-54	2,070	2,080	5,680	5,420	3,950	3,920
Age at starting to smoke						
<15	14.9	12.4	11.8	5.3	13.4	5.4
15-19	50.4	25.5	45.7	31.8	37.3	25.9
20-24	10.7	11.7	9.4	13.6	12.7	10.9
25+	6.6	8.8	7.1	7.6	4.2	6.1
Smokers, unclassified	1.7	2.9	5.5	1.5	7.7	2.7
Never smokers	15.7	38.7	20.5	40.2	24.6	49.0

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TABLE H-2 (continued)

	Eston		Stockton		Rural Districts	
	Male (%)	Female (%)	Male (%)	Female (%)	Male (%)	Female (%)
Number 55-64	1,910	1,720	4,150	4,330	3,420	3,770
Age at starting to smoke						
<15	18.6	2.3	20.0	5.2	10.8	1.6
15-19	43.3	11.5	30.0	17.7	35.1	12.6
20-24	15.5	13.8	11.1	6.3	7.2	8.7
25+	8.2	19.5	12.2	22.9	7.2	10.2
Smokers, unclassified	3.1	2.3	3.3	2.1	8.1	1.6
Never smokers	11.3	50.6	23.3	45.8	31.5	65.4
Number 65+	980	1,790	3,590	5,490	3,260	4,360
Age at starting to smoke						
<15	28.4	0.9	20.5	0.0	14.8	0.6
15-19	27.0	4.3	38.6	9.8	31.5	4.4
20-24	9.5	0.9	15.7	5.7	9.3	3.8
25+	9.5	12.9	10.8	12.3	6.5	9.5
Smokers, unclassified	2.7	0.0	2.4	2.5	8.3	1.3
Never smokers	23.0	81.0	12.0	69.7	29.6	80.4

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TABLE H-3

DISTRIBUTION OF DEPTH OF INHALATION BY DISTRICT AND SEX IN THE LIVING POPULATION, 1973

	Eston		Stockton		Rural Districts	
	Male (%)	Female (%)	Male (%)	Female (%)	Male (%)	Female (%)
Number 35+	7,230	7,570	18,370	20,460	15,380	16,510
Inhalation category						
A lot	36.8	17.5	29.0	12.2	22.8	9.0
A fair amount	17.6	10.3	19.7	11.8	15.5	11.6
A little	15.7	14.0	12.9	13.8	13.4	10.0
None	10.0	9.5	12.9	12.8	14.5	6.8
Smokers, unclassified	1.9	0.2	6.6	1.2	4.8	1.2
Never smokers	18.1	48.5	19.0	48.2	29.1	61.4

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TABLE H-4

PROPORTION OF MANUFACTURED-CIGARETTE SMOKERS WHO SMOKE FILTER CIGARETTES--BY AREA, SEX AND PERIOD FOR WHICH SMOKING HABITS REPORTED

	Eston		Stockton		Rural Districts	
Filter Smokers	Male (%)	Female (%)	Male (%)	Female (%)	Male (%)	Female (%)
Current	60.5	83.6	68.6	86.9	74.8	88.0
3-5 years ago	52.4	75.5	61.9	76.4	69.4	83.6
6-10 years ago	33.3	51.3	38.4	63.4	52.7	71.2
>10 years ago	9.9	23.6	18.2	35.4	30.8	45.8